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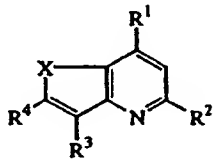
(54) Title: CRF ANTAGONISTIC THIOPHENOPYRIDINES

(57) Abstract

This invention concerns compounds of formula (I), including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein X is S or SO_2; R^1 is C_{1-6}alkyl, NR^5R^6, OR^6 or SR^6; R^2 is C_{1-6}alkyl, C_{1-6}alkyloxy or C_{1-6}alkylthio; R^3 is Ar^1 or Het^1; R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfoxy or C_{1-6}alkylthio; R^5 is hydrogen, C_{1-8}alkyl, mono– or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; R^6 is C_{1-8}alkyl, mono– or di(C_{3-6}cycloalkyl)methyl, Ar^2CH_2, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}alkenyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, mono– or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{1-6}alkyl; or R^5 and R^6 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; and Ar^1 and Ar^2 are each optionally substituted phenyl; and Het^1 is optionally substituted pyridinyl; having CRF receptor antagonistic properties; pharmaceutical compositions containing such compounds as active ingredients; methods of treating disorders related to hypersecretion of CRF such as depression, anxiety, substance abuse, by administering an effective amount of a compound of formula (I).



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CRF ANTAGONISTIC THIOPHENOPYRIDINES

Background of the invention

This invention relates to thiophenopyridines which possess CRF receptor antagonistic properties, to pharmaceutical compositions containing these compounds as active ingredient, and the use thereof in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalmi and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical, but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983). CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), β-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 221:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol. 124:560,* 1986; Wynn et al., *Biochem. Biophys. Res. Comm. 110:602-608,* 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118: 1171- 1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology 113:657-662,* 1983).

In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., J. *Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 2/8332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology 110:928,* 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology 110:2222,* 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggest that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990).

Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

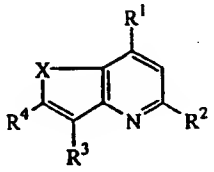
Due to the physiological significance of CRF, the development of further biologically active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

CRF receptor antagonists have been reported in for example, WO-94/13676, WO-94/13677 and WO-95/33750 which disclose pyrrolopyrimidines, pyrazolo[3,4-d]-pyrimidines and substituted purines as CRF receptor antagonists. EP-0,452,002 discloses thienopyrimidines having fungicidal, insecticidal and miticidal utility. Further, EP-0,209,977 discloses thienopyridones as antihypertensive agents.

The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the substituents on the thiophenopyridine moiety, and pharmacologically by the fact that, unexpectedly, these compounds have CRF antagonistic properties.

Description of the invention

This invention concerns compounds of formula (I)



(I),

including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S or SO_2;

R^1 is C_{1-6}alkyl; NR^5R^6, OR^6 or SR^6;

R^2 is C_{1-6}alkyl, C_{1-6}alkyloxy or C_{1-6}alkylthio;

R^3 is Ar^1 or Het^1;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

R^6 is C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, Ar^2CH_2, C_{1-6}alkyloxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}alkenyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{1-6}alkyl;

or R^5 and R^6 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; and

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6}alkyloxy, benzyloxy, C_{1-6}alkylthio, nitro, amino and mono- or di(C_{1-6}alkyl)amino;

Het^1 is pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6}alkyloxy, benzyloxy, C_{1-6}alkylthio, nitro, amino, and mono- or di(C_{1-6}alkyl)amino; and

Ar^2 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or trifluoromethyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-2}alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C_{2-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C_{3-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C_{1-6}alkyl includes C_{1-2}alkyl and C_{3-4}alkyl radicals as defined hereinbefore and the higher homologues thereof having from 5 to 6 carbon atoms such as, pentyl, the pentyl isomers, hexyl and the hexyl isomers; C_{1-8}alkyl includes C_{1-6}alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C_{3-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; and where said C_{3-6}alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C_{3-6}cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC_{1-6}alkyl refers to C_{1-6}alkyl substituted with a hydroxy group.

Depending on the nature of some of the substituents, the compounds of formula (I) may contain one or more asymmetric centers which may be designated with the generally used R and S nomenclature.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formula (I), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) wherein Het^1 is pyridinyl substituted with hydroxy, may exist in their corresponding tautomeric form.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to include also the pharmaceutically acceptable acid addition salts and all stereoisomeric forms.

Particular groups of compounds within the invention are those compounds of formula (I) wherein one or more of the following restrictions apply :

a) X is S or SO_2; in particular X is S;

b) R^1 is NR^5R^6 wherein R^5 is C_{1-8}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; in particular C_{2-4}alkyl or C_{1-2}alkyloxyC_{2-4}alkyl; and R^6 is C_{1-8}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^2CH_2 or C_{3-6}cycloalkylmethyl; in particular C_{2-4}alkyl, C_{1-2}alkyloxyC_{2-4}alkyl, phenylmethyl or cyclopropylmethyl;

c) R^2 is C_{1-6}alkyl; in particular C_{1-2}alkyl;

d) R^3 is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy or halo; wherein the phenyl moiety is preferably substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions; or R^3 is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, amino, nitro, trifluoromethyl, mono- or di(C_{1-6}alkyl)amino, piperidinyl or C_{1-6}alkyl; wherein the

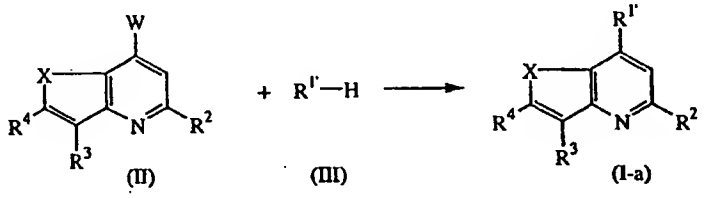
pyridinyl moiety preferably is connected via the 2- or 3-position to the remainder of the molecule;

e) R^4 is hydrogen or C_{1-6}alkyl; in particular R^4 is hydrogen or C_{1-2}alkyl.

Preferred compounds are those compounds of formula (I) wherein R^1 is NR^5R^6 and R^5 is C_{3-4}alkyl, preferably propyl; R^6 is C_{3-4}alkyl, phenylmethyl or cyclopropylmethyl, preferably propyl or phenylmethyl; R^2 is methyl; R^3 is a phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or methoxy; or R^3 is pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or dimethylamino; and R^4 is hydrogen.

Most preferred are those compounds selected from
2-methyl-6-(dipropylamino)-(2',4',6'-trimethylphenyl)-thiophenopyridine; and
2-methyl-6-(*N*-benzyl-*N*-propylamino)-(2',4',6'-trimethylphenyl)-thiophenopyridine;
the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

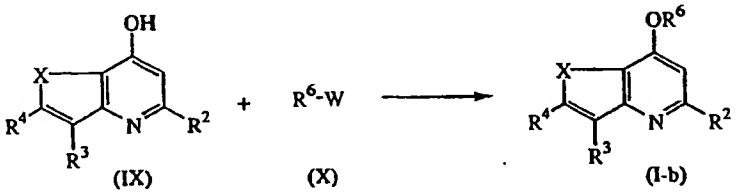
Compounds of formula (I-a), defined as compounds of formula (I) wherein $R^{1'}$ has the meaning of R^1 other than C_{1-6}alkyl, can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III). In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.



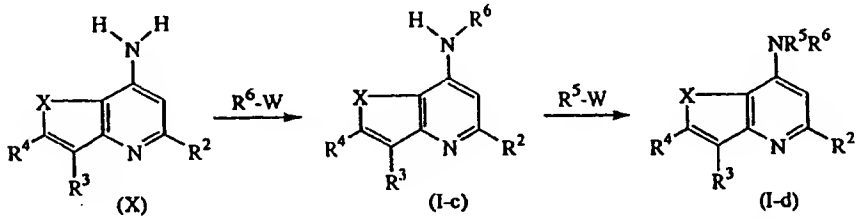
(II) (III) (I-a)

Said reaction can be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, methyl isobutylketone, tetrahydrofuran or dichloromethane; and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. When the intermediates of formula (III) are volatile amines, said reaction may also be performed in a sealed reaction vial. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature, and optionally is the presence of a suitable catalyst.

Also, compounds of formula (I) wherein R^1 is OR^6, said compounds being represented by formula (I-b), may be prepared by *O*-alkylating an intermediate of formula (IX) with an intermediate of formula (X), wherein W is as defined above. Said reaction can be performed in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, preferably at a temperature ranging between room temperature and reflux temperature.



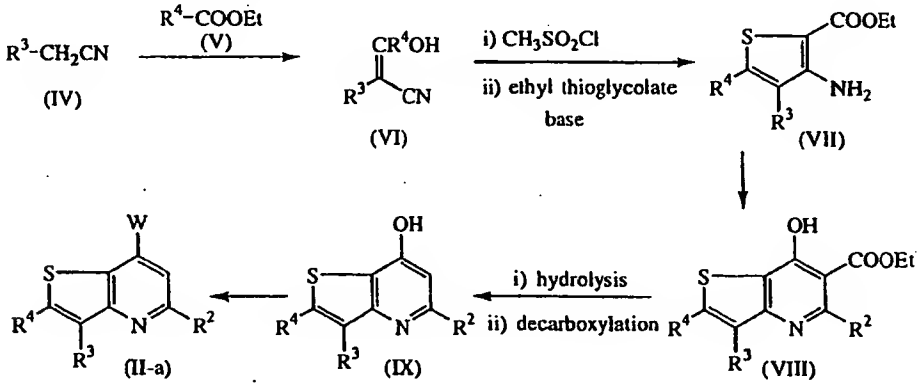
The compounds of formula (I) wherein R^1 is $-NHR^6$, represented by formula (I-c), can be prepared by *N*-alkylating an intermediate of formula (X) with an intermediate of formula R^6-W, wherein W is as previously defined. Compounds of formula (I-c) can be further *N*-alkylated with an intermediate of formula R^5-W, wherein W is as previously defined, yielding compounds of formula (I-d). These *N*-alkylations are conducted in a reaction-inert solvent such as, for example, an ether e.g. tetrahydofuran and preferably in the presence of a strong base, e.g. NaH.



As outlined below, compounds of formula (I) may be converted into each other following art-known functional group transformation procedures.

For instance, compounds of formula (I) wherein X is S can be converted into compounds of formula (I) wherein X is SO_2 by an oxidation reaction, e.g. treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane.

Intermediates of formula (II) wherein X is S, said intermediates being represented by compounds of formula (II-a), can be prepared as outlined herebelow. Intermediates of formula (VI) are prepared by treating intermediates of formula (IV) with an ester of formula (V) in a reaction-inert solvent such as an alcohol, e.g. ethanol, preferably in the presence of a strong base such as, e.g. sodium ethoxide or sodium hydride. The intermediates (VI) are reacted with methanesulphonyl chloride and subsequently with ethyl thioglycolate in the presence of an excess of a suitable base such as, e.g. potassium bis(trimethylsilyl)amide, yielding aminothiophene derivatives of formula (VII). These are cyclized into intermediates (VIII) under acidic conditions and in the presence of an intermediate of formula R^2-C(OEt)=CH-COOEt. Intermediates of formula (VIII) are converted to intermediates (IX) using art-known hydrolysis methods, for example stirring in the presence of a base, and subsequent decarboxylation, e.g. by heating in a reaction-inert solvent such as e.g. diphenyl ether. Intermediates of formula (IX) are converted to intermediates of formula (II-a) by treating intermediates (IX) with methanesulfonyloxy chloride or a halogenating reagent such as, e.g. $POCl_3$.



Intermediates of formula (X) are prepared by treating intermediates of formula (II) with ammonia.

Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be

converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* I:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (*e.g.* [^{125}I]tyrosine CFR) to receptor (*e.g.*, receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC_{50} as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation :

$$K_i = \frac{IC_{50}}{1 + L/K_D}$$

where L = radioligand and K_D= affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be

evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. *(supra,* 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza *(supra,* 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (supra, 1987)). With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM. In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1 μM, and more preferably less than 0.25 μM *(i.e.,* 250 nM).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurologic disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF

receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder, that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurologic disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorings, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the

present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

Hence, this invention provides the use of compounds of formula (I) for the manufacture of a medicine for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF) and in particular for treating the disorders or illnesses mentioned above; and in a further embodiment the use of novel compounds of formula (I) as a medicine is provided.

The following examples are provided for purposes of illustration, not limitation.

Experimental part

Hereinafter "THF" means tetrahydrofuran and "DCM" means dichloromethane.

A. Preparation of the intermediates.

Example A.1

a) A solution of 2,4,6-trimethylphenylacetonitrile (75 g) and ethyl formate (67 g) in 225 ml absolute ethanol was treated with solid sodium ethoxide (36 g) in small portions over 10 minutes, with good stirring. The mixture was heated to 60°C under nitrogen for 16 hours, was allowed to cool to room temperature, and then poured into 1.2 l of water. This mixture was extracted with ether. The aqueous phase was acidified with 6M HCl to pH 1 and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and brine, dried and concentrated to give 46 g of 3-hydroxy-2-(2',4',6'-trimethylphenyl)acrylonitrile (intermediate 2). A sample was crystallized from ether/hexane to give colorless crystals, melting point = 124-126°C.

b) A solution of intermediate (2) (1 g, 5.3 mmol) in 10 ml pyridine was cooled to 0°C under nitrogen and then treated with methanesulfonyl chloride (0.67 g) with good stirring. The solution was stirred for 1 hour and then poured into water. This mixture was extracted with ethyl acetate. The organic phase was washed with 1M HCl, water and brine, dried and then concentrated to give 1.42 g of 3-methanesulfonoxy-2-(2',4',6'-trimethylphenyl)acrylonitrile (intermediate 3) as a brown solid. A sample was crystallized from ether/hexane to give colorless crystals, melting point = 97-98°C.

c) A solution of intermediate (3) (1 g) in 40 ml of THF was treated with ethyl thioglycolate (0.45 g). This solution was treated with potassium bis(trimethylsilyl)-

amide (0.5M in toluene, 23 ml) via syringe. The reaction was allowed to stir overnight, and then poured into dilute aqueous HCl. The mixture was extracted with ethyl acetate, the organic phase was washed with 5% $NaHCO_3$, then brine, dried and concentrated. The crude mixture was crystallized from ether/hexane to give 1.0 g of 2-carboxy-3-amino-4-(2,4,6-trimethylphenyl)-thiophene, ethyl ester (intermediate 4).

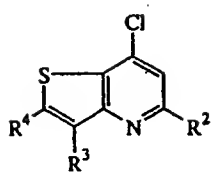
d) A solution of intermediate (4) (1.5 g) and 75 mg p-toluenesulfonic acid monohydrate in 50 ml xylene and 3-ethoxy-ethylcrotonate (823 mg, 5.2 mmol) was stirred and heated to reflux under nitrogen. Solvent (25 ml) was removed by slow distillation over 1 hour. The solution was allowed to cool to room temperature and a solution of potassium *tert*-butoxide (570 mg) in 12 ml of absolute ethanol was added. This mixture was heated to 80°C for 2 hours. This was allowed to cool to room temperature, treated with 0.6 ml acetic acid then concentrated to dryness. The residue was suspended in ethyl acetate stirred, filtered and washed to remove all the product from the potassium acetate. The filtrate was concentrated to a small volume and treated with diethyl ether to crystallize 1.7 g of 1-carboxy-2-methyl-6-hydroxy-8-(2',4',6'-trimethylphenyl)thiopheno-pyridine, ethyl ester (intermediate 5).

e) A solution of intermediate (5) (1.7 g) and 17.5 ml of 1M LiOH in 10 ml ethanol was stirred and heated to reflux under nitrogen for 16 hours. The solution was allowed to cool to room temperature then poured into a mixture of 15 ml of 1M hydrochloric acid in 100 ml of water. This was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated to give 1-carboxy-2-methyl-6-hydroxy-8-(2',4',6'-trimethylphenyl)thiopheno-pyridine (intermediate 6). This was used directly in the next step.

f) A solution of intermediate (6) (400 mg) in 0.4 ml diphenyl ether was stirred and heated to 230°C for 1.5 hour. The solution was allowed to cool to room temperature and 0.8 ml of $POCl_3$ was added. This mixture was heated to 100°C for 2 hours, then allowed to cool to room temperature, and poured into 5% $NaHCO_3$. This was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated. The product was purified by flash chromatography (SiO_2) using 0 to 10% ether/hexane, to give 210 mg of 2-methyl-6-chloro-8-(2',4',6'-trimethylphenyl)thiophenopyridine (intermediate 1). ^1H NMR ($CDCl_3$) : δ 2.02 (s, 6H), 2.36 (s, 3H), 2.59 (s, 3H), 5.25 (bs, 2H), 6.99 (s, 2H), 7.19 (s, 1H), 7.50 (s, 1H). Melting point = 129-131°C.

Table 1 lists the intermediates that were prepared according to one of the above Examples.

Table I-1 :



NBI	Intm. No.	Ex. No.	R^2	R^4	R^3
31220	1	A.1	CH_3	H	2,4,6-trimethylphenyl

B. Preparation of the final compounds.

Example B.1

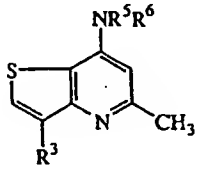
A mixture of intermediate 1 (10 mg), p-toluenesulfonic acid (20 mg) and dipropylamine (50 µl) was stirred and heated to 195°C for 1.5 hour. The solution was allowed to cool to room temperature, then dissolved in a mixture of water and ethyl acetate. This was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated. The product was purified by preparative TLC (SiO_2) using ethyl acetate/hexane, to give the 2-methyl-6-(dipropylamino)-2',4',6'-trimethylphenyl)-thiophenopyridine (compound 1).

Example B.2

Intermediate 1 (10 mg) in DMSO (0.2 ml) was treated with di-n-propylamine (0.1 ml) and tetraethylammonium iodide (9 mg) at 195°C for 3.5 hours. The reaction was diluted with ethyl acetate and water and the organic layer was purified by silica gel preparative thin layer chromatography (ethyl acetate:hexane 2:3). Compound 6 was isolated and a small amount of compound 8 was also isolated.

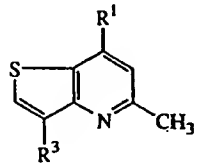
Tables F-1 and F-2 list the compounds that were prepared according to one of the above Examples and table F-3 lists the analytical data for these compounds.

Table F-1 :



Co. No.	Ex. No.	R^5	R^6	R^3
1	B.1	n-propyl	n-propyl	2,4,6-trimethylphenyl
2	B.1	ethyl	n-butyl	2,4,6-trimethylphenyl
3	B.1	n-propyl	cyclopropylmethyl	2,4,6-trimethylphenyl
4	B.1	n-propyl	phenylmethyl	2,4,6-trimethylphenyl
5	B.1	2-methoxyethyl	2-methoxyethyl	2,4,6-trimethylphenyl
6	B.1	n-propyl	n-propyl	2,4-dichlorophenyl
7	B.1	2-methoxyethyl	2-methoxyethyl	2,4-dichlorophenyl

Table F-2 :



Co. No.	Ex. No.	R^1	R^3
8	B.2	CH_3-S-	2,4,6-trimethylphenyl

Table F-3 : Analytical data

Co. No.	Mass spectral data	Co. No.	Mass spectral data
1	366 (M^+)	5	398 (M^+)
2	366 (M^+)	6	392 (M^+)
3	378 (M^+)	7	424 (M^+)
4	414 (M^+)	8	313 (M^+)

C. Pharmacological examples

Example C.1 : CRF receptor binding activity

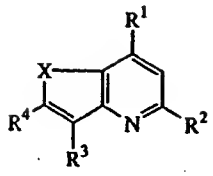
Compounds were evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by DeSouza et al. (*J. Neurosci.* 7:88-100, 1987). By utilizing various radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype. Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor.

More specifically, the binding assay was performed in 1.5 ml Eppendorf tubes using approximately 1 x 10^6 cells per tube stably transfected with human CRF receptors. Each tube received about 0.1 ml of assay buffer *(e.g.,* Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 µM bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 µM) to determine nonspecific binding, 0.1 ml of [^{125}I] tyrosine - ovine CRF (final concentration ~200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane suspension of cells containing the CRF receptor. The mixture was incubated for 2 hours at 22°C followed by the separation of the bound and free radioligand by centrifugation. Following two washes of the pellets, the tubes were cut just above the pellet and monitored in a gamma counter for radioactivity at approximately 80% efficiency. All radioligand binding data was analyzed using a non-linear least-square curve-fitting program.

Binding activity corresponds to the concentration (nM) of the compound necessary to displace 50% of the radiolabeled ligand from the receptor. Compounds 1 to 8 have a $K_i \leq 250$ nM. Compounds 2 to 7 were found to show the best score in this test.

Claims

1. A compound of formula



(I),

including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S or SO_2;

R^1 is C_{1-6}alkyl; NR^5R^6, OR^6 or SR^6;

R^2 is C_{1-6}alkyl, C_{1-6}alkyloxy or C_{1-6}alkylthio;

R^3 is Ar^1 or Het^1;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, C_{3-6}cycloalkyl, C_{3-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

R^6 is C_{1-8}alkyl, mono- or di(C_{3-6}cycloalkyl)methyl, Ar^2CH_2, C_{1-6}alkyloxy-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}alkenyl, thienylmethyl, furanylmethyl, C_{1-6}alkylthioC_{1-6}alkyl, mono- or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonylC_{1-6}alkyl;

or R^5 and R^6 taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl; and

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6}alkyloxy, benzyloxy, C_{1-6}alkylthio, nitro, amino and mono- or di(C_{1-6}alkyl)amino;

Het^1 is pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, trifluoromethyl, hydroxy, cyano, C_{1-6}alkyloxy, benzyloxy, C_{1-6}alkylthio, nitro, amino, and mono- or di(C_{1-6}alkyl)amino; and

Ar^2 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, or trifluoromethyl.

2. A compound according to claim 1 wherein R^1 is NR^5R^6 wherein R^5 is C_{1-8}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl, and R^6 is C_{1-8}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^2CH_2 or C_{3-6}cycloalkylmethyl; R^2 is C_{1-6}alkyl; R^3 is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy or halo, or R^3 is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl or di(C_{1-6}alkyl)amino; and R^4 is hydrogen or C_{1-6}alkyl.

3. A compound according to any of claims 1 to 2 wherein R^1 is NR^5R^6 wherein R^5 is C_{2-4}alkyl or C_{1-2}alkyloxyC_{2-4}alkyl and R^6 is C_{2-4}alkyl, C_{1-2}alkyloxyC_{2-4}alkyl, cyclopropylmethyl or phenylmethyl; R^2 is C_{1-2}alkyl; R^3 is phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-2}alkyl, C_{1-2}alkyloxy or halo; R^4 is hydrogen or C_{1-2}alkyl.

4. A compound according to any of claims 1 to 2 wherein R^1 is NR^5R^6 wherein R^5 is C_{2-4}alkyl and R^6 is C_{3-4}alkyl, phenylmethyl, methoxyethyl or cyclopropylmethyl; R^2 is methyl; R^3 is 2,4,6-trimethylphenyl; and R^4 is hydrogen or methyl.

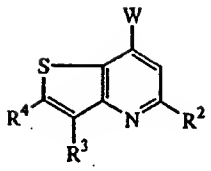
5. A compound according to claim 1 wherein the compound is 2-methyl-6-(dipropylamino)-(2',4',6'-trimethylphenyl)-thiophenopyridine; or 2-methyl-6-(*N*-benzyl-*N*-propylamino)-(2',4',6'-trimethylphenyl)-thiophenopyridine; a stereochemically isomeric form, or a pharmaceutically acceptable acid addition salts thereof.

6. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

7. A process for preparing a composition as claimed in claim 6 wherein a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 5 for use as a medicine.

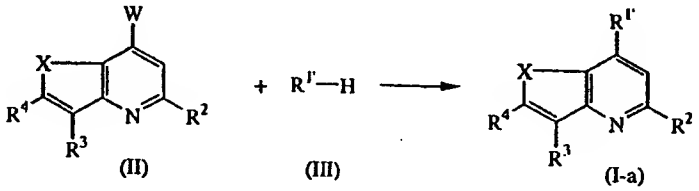
9. A compound of formula (II-a) wherein the radicals R^2, R^3 and R^4 are as defined in claim 1 and W is halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof.



(II-a)

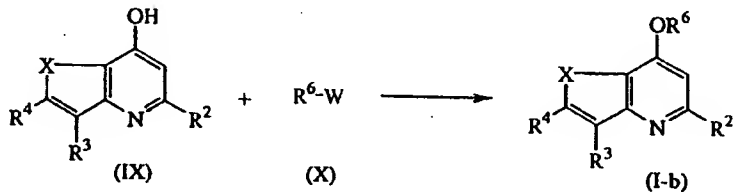
10. A process of preparing a compound of formula (I) as claimed in claim 1 wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III), wherein $R^{1'}$ has the meaning of R^1 other than C_{1-6}alkyl, thereby yielding compounds of formula (I-a);



(II) (III) (I-a)

b) an intermediate of formula (IX) is *O*-alkylated with an intermediate of formula (X) in a reaction-inert solvent and in the presence of a suitable base, yielding compounds of formula (I-b), defined as compounds of formula (I) wherein R^1 is OR^6,

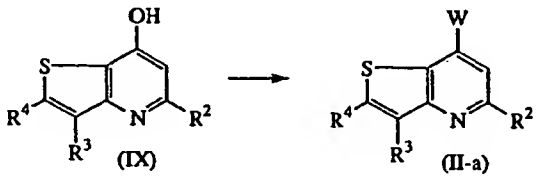


(IX) (X) (I-b)

wherein in the above reaction schemes the radicals R^1, R^2, R^3, R^6 and X are as defined in claim 1 and W is an appropriate leaving group;

or, if desired, compounds of formula (I) are converted into each other following art-known transformation reactions; and further, if desired, compounds of formula (I) are converted into an acid addition salt by treatment with an acid, or conversely, the acid addition salt forms are converted into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

11. A process of preparing a compound of formula (II-a) as claimed in claim 9 wherein a) an intermediate of formula (IX) is treated with methanesulfonyloxy chloride, benzenesulfonyloxy chloride or a halogenating reagent such as, e.g. $SOCl_2$ or $POCl_3$;



wherein in the above reaction scheme the radicals R^2, R^3 and R^4 are as defined in claim 1 and W is halo, mesyloxy or tosyloxy;

or, if desired, compounds of formula (II-a) are converted into each other following art-known transformation reactions; and further, if desired, compounds of formula (II-a) are converted into an acid addition salt by treatment with an acid, or conversely, the acid addition salt forms are converted into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

12. A method of antagonizing a CRF receptor in a warm-blooded animal, comprising administering to the animal an effective amount of a compound of any of claims 1 or 5.

13. A method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal an effective amount of a compound of any of claims 1 or 5.

14. The method of claim 13 wherein the disorder is selected from depression, an anxiety-related disorder, a feeding disorder, stress-induced immune suppression, stroke, Cushing's disease, infantile spasms, epilepsy, seizure, an inflammatory condition.

15. The method of claim 14 wherein the feeding disorder is anorexia nervosa, bulimia or irritable bowel syndrome.

INTERNATIONAL SEARCH REPORT

Interna... al Application No
PCT/EP 98/02268

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D495/04 A61K31/44 A61K31/38 //(C07D495/04,333:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 35689 A (NEUROGEN CORP ;YUAN JUN (US); HUTCHISON ALAN (US)) 14 November 1996 see the whole document; in particular claims 1, 4, 28, 29 and 41	1-15
P,X	WO 98 08847 A (PFIZER ;CHEN YUHPYNG LIANG (US)) 5 March 1998 see the whole document; in particular page 7, formula I-H and page 16, lines 20-25	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 1998	11.09.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Fink, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/02268

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/EP 98/02268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9635689 A	14-11-1996	US 5644057 A	01-07-1997
		AU 5679096 A	29-11-1996
		CA 2194756 A	14-11-1996
		EP 0770080 A	02-05-1997
		JP 10506126 T	16-06-1998
WO 9808847 A	05-03-1998	AU 3456197 A	19-03-1998

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(54) Title: TETRAHYDROPYRIDINO OR PIPERIDINO HETEROCYCLIC DERIVATIVES

(57) Abstract: A tetrahydropyridino or piperidino heterocyclic derivative represented by the formula [I]: A-Het [I]has a high affinity for CRF receptors and is effective against diseases in which CRF is considered to be involved.

DESCRIPTION

TETRAHYDROPYRIDINO OR PIPERIDINO HETEROCYCLIC DERIVATIVES

TECHNICAL FIELD

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, etc.

BACKGROUND ART

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995). For CRF, there are the following two paths: a path by which CRF acts on peripheral immune system or sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in central nervous

system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in central nervous system.

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, antagonists against CRF receptors are useful as therapeutic agents for the diseases described above.

An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for

diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug-dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, etc.

DISCLOSURE OF THE INVENTION

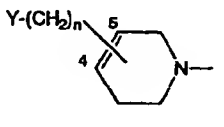
The present inventors earnestly investigated tetrahydropyridino or piperidino heterocyclic derivatives and consequently found novel tetrahydropyridino or piperidino heterocyclic derivatives having a high affinity for CRF receptors, whereby the present invention has been accomplished.

The present invention is explained below.

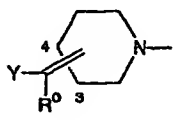
The present invention is a tetrahydropyridino or piperidino heterocyclic derivative represented by the following formula [I]:

A-Het [I]

wherein A is a group represented by the following formula [II] or [III]:



[II]



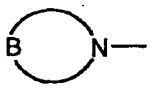
[III]

wherein the position of substitution by the $Y-(CH_2)_n-$ group of the group represented by the formula [II] is 4-position or 5-position, the position of substitution by the $Y-C(R^0)=$ group of the group represented by the formula [III] is 3-position or 4-position,

R^0 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group,

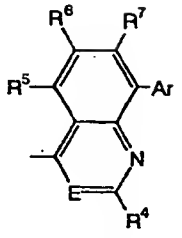
n is an integer of 0 to 5, and

Y is a cyano group, a group represented by the formula $-CONR^1(R^2)$ (wherein each of R^1 and R^2, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{1-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group, or R^1 and R^2, when taken together with the adjacent nitrogen atom, represent a 5- to 8-membered saturated heterocyclic group represented by the formula:



(wherein B is CH_2, NH, N-C_{1-5}alkyl, N-C_{3-8}cycloalkyl, N-C_{1-5}alkyl-C_{3-8}cycloalkyl, O or S)) or a group represented by the formula $-CO_2R^3$ (wherein R^3 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{1-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group), and

Het is any of heterocyclic groups represented by the following formulas form(01) to form(20):



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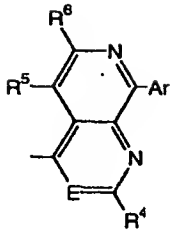

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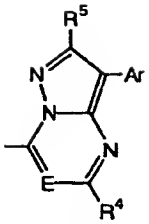

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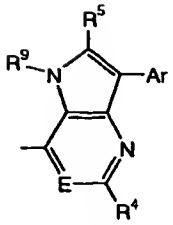

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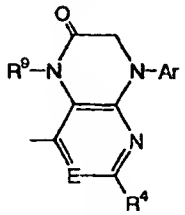

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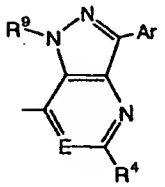

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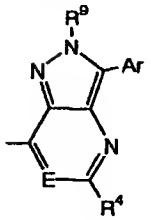

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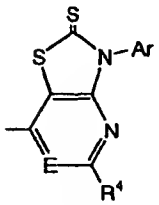

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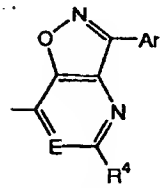

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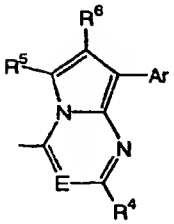

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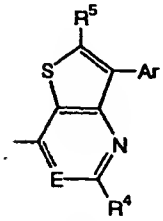

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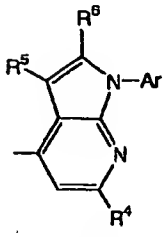

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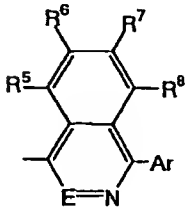
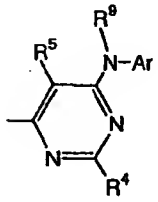


form(13)



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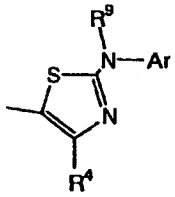

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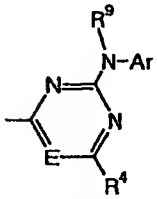

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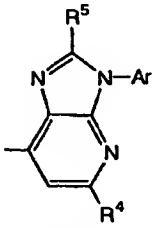

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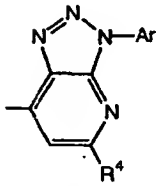

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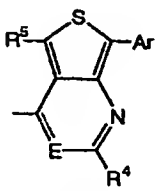

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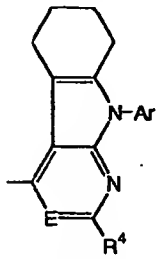


form(20)

wherein E is CH or N,

R^4 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a hydroxyl group, a C_{1-5}alkoxy group, a C_{3-8}cycloalkyloxy group, or a group represented by the formula $-N(R^{10})R^{11}$ (wherein each of R^{10} and R^{11}, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group),

each of R^5, R^6, R^7 and R^8, which may be the same or different, is a hydrogen atom, a halogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a hydroxyl group, a C_{1-5}alkoxy group, a C_{3-8}cycloalkyloxy group, a group represented by the formula $-N(R^{12})R^{13}$ (wherein each of R^{12} and R^{13}, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group), a group represented by the formula $-CO_2R^{14}$ (wherein R^{14} is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{1-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group), a cyano group, a nitro group, a C_{1-5}alkylthio group, a trifluoromethyl group or a trifluoromethoxy group,

R^9 is a hydrogen atom, a C_{1-5}alkyl group, a C_{2-5}alkenyl group, a C_{2-5}alkynyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group, and

Ar is an aryl or heteroaryl group unsubstituted or substituted with 1 to 3 substituents which may

be the same or different and are selected from halogen atoms, C_{1-5}alkyl groups, C_{1-5}alkoxy groups, C_{1-5}alkylthio groups, trifluoromethyl group, trifluoromethoxy group and groups represented by the formula $-N(R^{15})R^{16}$ (wherein each of R^{15} and R^{16}, which may be the same or different, is a hydrogen atom or a C_{1-5}alkyl group); or a pharmaceutically acceptable salt thereof or its hydrate.

The terms used in the present specification have the following meanings.

The term "C_{1-5}alkyl group" means a straight chain or branched chain alkyl group of 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl or the like. The term "C_{2-5}alkenyl group" means a straight chain or branched chain alkenyl group of 2 to 5 carbon atoms, such as vinyl, 1-propenyl, 2-propenyl, 1-methylvinyl or the like. The term "C_{2-5}alkynyl group" means a straight chain or branched chain alkynyl group of 2 to 5 carbon atoms, such as ethynyl, 2-propynyl or the like. The term "C_{3-8}cycloalkyl group" means a cyclic alkyl group of 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like. The term "C_{3-8}cycloalkyl-C_{1-5}alkyl group" means a substituted C_{1-5}alkyl group having the above-mentioned C_{3-8}cycloalkyl group as the substituent, such as cyclopropylmethyl, cyclopropylethyl, cyclopentylethyl or the like.

For B, the term "N-C_{1-5}alkyl" means a group having a C_{1-5}alkyl group as a substituent on the nitrogen

atom. The term "N-C_{3-8}cycloalkyl" means a group having a C_{3-8}cycloalkyl group as a substituent on the nitrogen atom. The term "N-C_{1-5}alkyl-C_{3-8}cycloalkyl" means a group having a C_{3-8}cycloalkyl-C_{1-5}alkyl group as a substituent on the nitrogen atom.

The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom. The term "C_{1-5}alkoxy group" means a straight chain or branched chain alkoxy group of 1 to 5 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like. The term "C_{3-8}cycloalkyloxy group" means a cyclic alkoxy group of 3 to 8 carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or the like. The term "C_{1-5}alkoxy-C_{1-5}alkyl group" means a substituted C_{1-5}alkyl group having a C_{1-5}alkoxy group as the substituent, such as methoxymethyl, 2-ethoxyethyl or the like. The term "C_{3-8}cycloalkyloxy-C_{1-5}alkyl group" means a substituted C_{1-5}alkyl group having a C_{3-8}cycloalkoxy group as the substituent, such as cyclopropyloxymethyl, 2-cyclopropyloxyethyl or the like. The term "C_{1-5}alkylthio group" means a straight chain or branched chain alkylthio group of 1 to 5 carbon atoms, such as methylthio, ethylthio, propylthio or the like.

The term "aryl group" means a phenyl group, a naphthyl group or the like. The term "heteroaryl group" means a heterocyclic group having in its ring 1 to 4 atoms which may be the same or different and are

selected from nitrogen, oxygen and sulfur, such as pyridyl, quinolyl, indolyl, benzofuranyl, benzothiadiazolyl, benzofurazanyl, quinoxalinyl or the like. Therefore, the substituted aryl or heteroaryl group includes, for example, 2,4,6-trimethylphenyl group, 2,4,6-tribromophenyl group, 2,4-dibromo-6-chlorophenyl group, 2,4-dichlorophenyl group, 2,4,6-trichlorophenyl group, 2-methyl-4-methoxyphenyl group, 2,4-dibromo-6-fluorophenyl group, 2,4-dibromo-6-methylphenyl group, 2,4-dibromo-6-methoxyphenyl group, 2,4-dibromo-6-methylthiophenyl group, 2,6-dibromo-4-isopropylphenyl group, 2,6-dibromo-4-trifluoromethylphenyl group, 2-chloro-4-trifluoromethylphenyl group, 2-chloro-4-trifluoromethoxyphenyl group, 6-dimethylamino-4-methylpyridin-3-yl group, 2-chloro-6-trifluoromethylpyridin-3-yl group, 2-chloro-6-trifluoromethoxypyridin-3-yl group, 2-chloro-6-methoxypyridin-3-yl group, 2-trifluoromethyl-6-methoxypyridin-3-yl group, 2-chloro-6-difluoromethylpyridin-3-yl group, 2-methyl-6-methoxypyridin-3-yl group, 2,6-dimethoxypyridin-3-yl group, 5,7-dimethyl-2,1,3-benzothiadiazol-4-yl group, 5,7-dimethylbenzofurazan-4-yl group, 6,8-dimethylquinoxalin-5-yl group, 5,7-dichloro-2,1,3-benzothiadiazol-4-yl, 5,7-dichlorobenzofurazan-4-yl group and 6,8-dichloroquinoxalin-5-yl group.

The pharmaceutically acceptable salt in the present invention includes, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric

acid, phosphoric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid or the like; and salts with a metal ion such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion or the like.

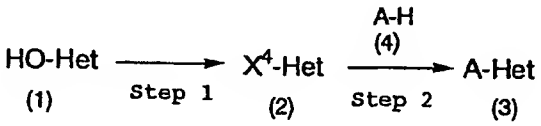
Preferable examples of the compound of the present invention are as follows.

That is, preferable are compounds of the formula [I] in which A is a group represented by the formula [II]. More preferable are compounds of the formula [I] in which A is a group represented by the formula [II], Y is a carbamoyl group and n is 0 or 1. In addition, preferable are compounds of the formula [I] in which Het is a heterocyclic group represented by form(01) or form(12). More preferable are compounds of the formula [I] in which Het is a heterocyclic group represented by form(01) or form(12), and Ar is a phenyl group having two or three substituents which may be the same or different and are selected from halogen atoms, C_{1-5}alkyl groups, C_{1-5}alkoxy groups, C_{1-5}alkylthio groups, trifluoromethyl group and trifluoromethoxy group. Still more preferable are compounds of the formula [I] in which Het is a heterocyclic group represented by form(01) or form(12), and Ar is a phenyl group having two or three substituents which may be the same or different and are selected from chlorine atom,

trifluoromethyl group and trifluoromethoxy group.

The compound of the formula [I] can be produced, for example, by any of the processes shown in the following reaction schemes 1 to 7 (in the following reaction schemes, A, Het, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above, R^{17} is a C_{1-5}alkyl group or a phenyl group, and X^4 is a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group, a benzenesulfonyloxy group, a toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group).

Reaction Scheme 1.



Step 1:

Compound (2) can be obtained by halogenation or sulfonylation of the hydroxyl group of Compound (1). Here, the halogenation refers to reaction with a halogenating reagent such as phosphorus oxychloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride, thionyl bromide, oxalyl chloride or the like in the presence or absence of, for example, N,N-dimethylaniline or N,N-diethylaniline without a solvent or in an inert solvent such as a hydrocarbon (e.g., benzene and toluene) or a halogen-containing solvent (e.g., chloroform and dichloromethane). The sulfonylation refers to reaction with a sulfonylating reagent

such as methanesulfonyl chloride, p-toluenesulfonyl chloride, trifluoromethanesulfonic acid anhydride, N-phenylbis(trifluoromethanesulfonimide) or the like in the presence or absence of a base in an inert solvent such as an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene), an amide (e.g., N,N-dimethylformamide and N-methylpyrrolidone), acetonitrile, dimethyl sulfoxide, pyridine, or a mixture of solvents selected from these inert solvents. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the like; and inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like.

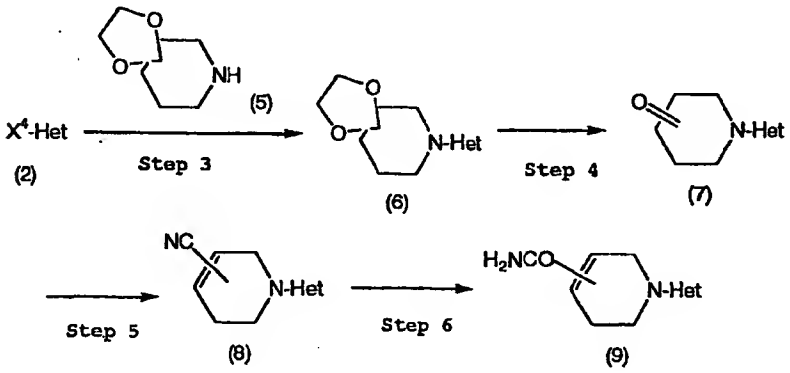
Step 2:

Compound (3), the compound of the present invention, can be obtained by reacting Compound (2) with Compound (4) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, amines such as triethylamine, diisopropyl-ethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide,

sodium ethoxide, potassium tert-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Compound (9) of the present invention can be synthesized according also to the following reaction scheme 2.

Reaction Scheme 2



Step 3:

Compound (6) can be obtained by reacting Compound (2) with Compound (5) in an inert solvent in

the presence or absence of a base. Here, the base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Step 4:

Compound (6) can be converted to Compound (7) by removing the acetal protective group of Compound (6) by conventional hydrolysis under acidic conditions (see Theodora W. Greene and Peter G. W. Wuts "Protective Groups in Organic Synthesis").

Step 5:

Compound (7) can be converted to Compound (8) by reacting Compound (7) in the presence of a cyanating agent such as sodium cyanide, potassium cyanide, trimethylsilyl cyanide or the like in an inert solvent such as an alcohol (e.g., methanol, ethanol, isopropyl alcohol and ethylene glycol), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), acetonitrile, acetic acid, water, or a mixture of solvents selected from these inert solvents; and then reacting the cyanation product with, for example, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoroacetic anhydride in the presence or absence of an organic base such as pyridine, triethylamine or diisopropylethylamine in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene) or the like.

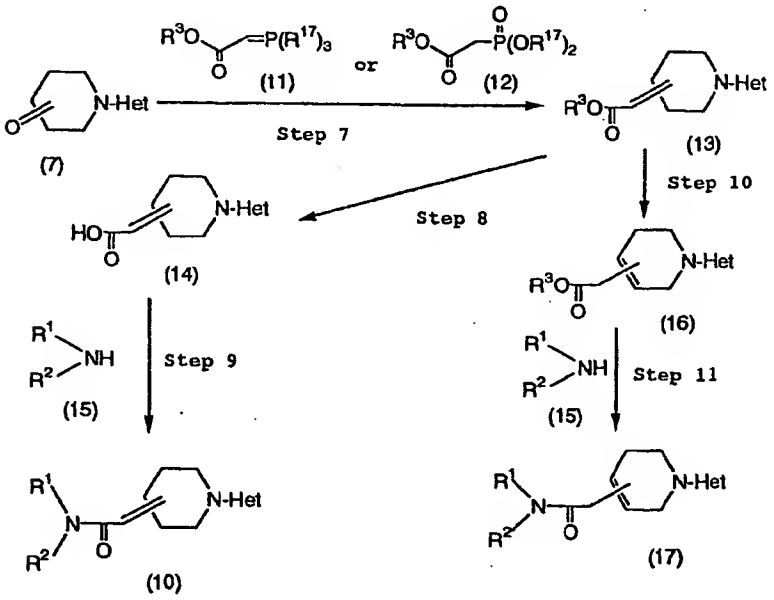
Step 6:

Compound (8) can be converted to Compound (9) of the present invention by reacting the cyano group of Compound (8) by using, for example, sulfuric acid, hydrogen chloride and formic acid singly or in combination of two or more thereof, in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane

and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene), water or a mixture of solvents selected from these inert solvents.

In addition, Compound (10) and Compound (17) of the present invention can be obtained according also to the following reaction scheme 3.

Reaction Scheme 3



Step 7:

Compound (7) can be converted to Compound (13) by reacting Compound (7) with either Compound (11) or Compound (12) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, sodium hydride, potassium hydride, sodium

methoxide, potassium tert-butoxide, n-butyllithium, lithium bis(trimethylsilyl)amide, sodium amide and potassium carbonate. If necessary, 18-crown-6 ether, 15-crown-5 ether, tetramethylethylenediamine, hexamethylphosphoramide and the like can be used as an additive. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; water; and mixtures of solvents selected from these inert solvents.

Step 8:

When R^3 of Compound (13) is a group other than a hydrogen atom, Compound (13) can be converted to Compound (14) of the present invention by conventional hydrolysis of the ester portion under acidic or basic conditions (see Theodora W. Greene and Peter G. W. Wuts "Protective Groups in Organic Synthesis").

Step 9:

Compound (10) of the present invention can be obtained by amidation of Compound (14). Here, the amidation refers to general amidation of the carboxyl group, and refers to any of the following reactions:

the reaction of Compound (15) with a mixed acid anhydride obtained by the reaction of Compound (14) with a haloformic acid ester (e.g., ethyl chloroformate and isobutyl chloroformate) or an acid halide (e.g., benzoyl chloride and pivaloyl chloride) in the presence of a base such as N-methylmorpholine, triethylamine or the like; the reaction of Compound (14) with Compound (15) in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (EDC), carbonyl-diimidazole (CDI), diphenylphosphorylazide (DPPA), diethyl cyanophosphate or the like and optionally an additive such as 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide, 4-dimethylaminopyridine or the like; and the reaction of Compound (15) with an acid halide obtained by the reaction of Compound (14) with a halogenating reagent such as thionyl chloride, oxalyl chloride, carbon tetrabromide-triphenylphosphine or the like.

Step 10:

Compound (13) can be converted to Compound (16) by reacting Compound (13) in the presence of an acid or a base in an inert solvent. Here, the acid includes, for example, inorganic acids such as hydrogen chloride, hydrobromic acid, sulfuric acid and the like; and organic acids such as acetic acid, trifluoroacetic acid, p-toluenesulfonic acid and the like. The base

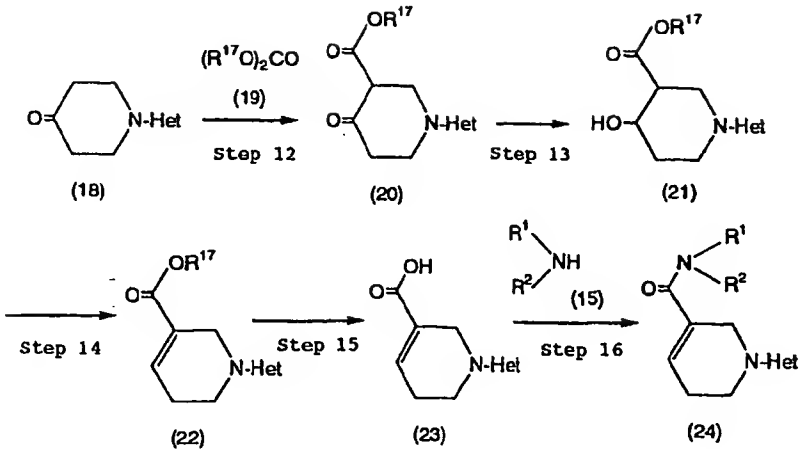
includes inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methyl-pyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; water; acetone; and mixtures of solvents selected from these inert solvents. When R^3 is a group other than a hydrogen atom, employment of a solvent for reaction composed of water alone or a mixture of water and one or more other solvents makes it possible to carry out the conversion of R^3 to a hydrogen atom and the conversion of Compound (13) to Compound (16) simultaneously.

Step 11:

When R^3 is a group other than a hydrogen atom, R^3 is converted to a hydrogen atom by the same procedure as in Step 8, after which Compound (17) of the present invention can be obtained by the same reaction as in Step 9.

Compounds (22), (23) and (24) can be synthesized according also to the following reaction scheme 4.

Reaction Scheme 4



Step 12:

Compound (20) can be obtained by reacting Compound (18) with Compound (19) in an inert solvent in the presence of a base. Here, the inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as ethanol, methanol and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; tetramethylurea; dimethyl sulfoxide; and mixtures of solvents selected from these inert solvents. The base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine and the like; inorganic bases such as sodium hydride, potassium hydride, sodium carbonate and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkyl metals such as n-butyllithium, tert-butyllithium, phenyllithium and

the like; and metal amides such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium amide and the like.

Step 13:

Compound (20) can be converted to Compound (21) by reduction of the ketone portion represented by hydride reduction using sodium boron hydride, and hydrogenation (see Ahmed F. Abdel-Magid "Reductions in Organic Synthesis").

Step 14:

Compound (21) can be converted to Compound (22) by reacting Compound (21) with, for example, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoroacetic anhydride in the presence or absence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane and chloroform), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene) or the like, or by reacting Compound (21) with, for example, sulfuric acid, trifluoroacetic acid or formic acid in an inert solvent such as a halogen-containing solvent (e.g., dichloromethane and chloro-

form), an ether (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane), a hydrocarbon (e.g., benzene and toluene) or the like.

Step 15:

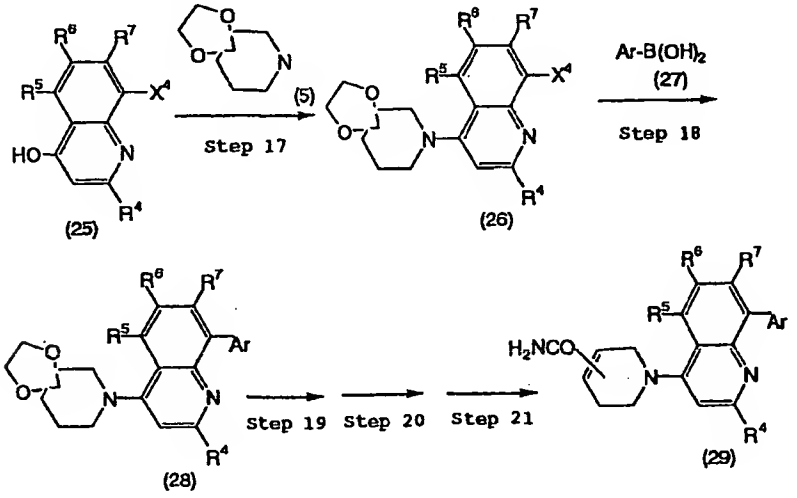
Compound (22) can be converted to Compound (23) of the present invention by converting the ester portion of Compound (22) to a carboxyl group by the same procedure as in Step 8.

Step 16:

Compound (23) can be converted to Compound (24) of the present invention by reacting Compound (23) with Compound (15) by the same procedure as in Step 9.

Compound (29) of the present invention can be synthesized according also to the following reaction scheme 5.

Reaction Scheme 5



Step 17:

Compound (26) can be obtained by halogenating or sulfonylating the hydroxyl group of Compound (25) by the same procedure as in Step 1, and then reacting the halogenation or sulfonylation product with Compound (5) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the like; and inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; and mixtures of solvents selected from these inert solvents.

Step 18:

Compound (26) can be converted to Compound (28) by reacting Compound (26) with an aryl-boric acid derivative (27) in an inert solvent in the presence of a base, a zero-valence palladium complex (e.g., tetrakis(triphenylphosphine)palladium and tetrakis-(tributylphosphine)palladium) or a divalent palladium

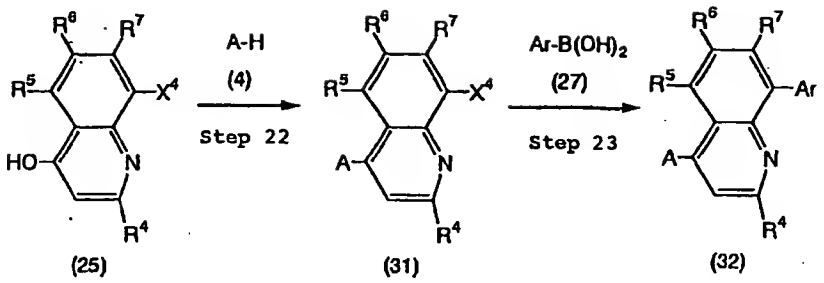
complex (e.g., palladium acetate and palladium chloride) and optionally a phosphine (e.g., triphenylphosphine and tributylphosphine). Here, the base includes, for example, inorganic bases such as sodium carbonate, sodium hydrogencarbonate, potassium carbonate, barium hydroxide, sodium hydroxide and the like; and organic bases such as triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like. The inert solvent includes, for example, halogen-containing solvents such as dichloromethane, chloroform and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; alcohols such as methanol, ethanol and the like; water; and mixtures of solvents selected from these inert solvents.

Step 19, Step 20 and Step 21:

Compound (29) of the present invention can be obtained by carrying out Step 19, Step 20 and Step 21 in the same manner as for Step 4, Step 5 and Step 6, respectively.

Compound (32) of the present invention can be synthesized according also to the following reaction scheme 6.

Reaction Scheme 6



Step 22:

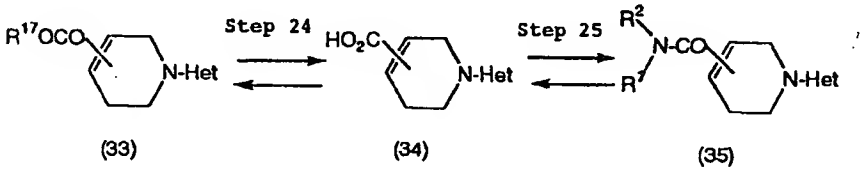
Compound (31) can be obtained by halogenating or sulfonylating the hydroxyl group of Compound (25) by the same procedure as in Step 1, and then reacting the halogenation or sulfonylation product with Compound (4) in an inert solvent in the presence or absence of a base. Here, the base includes, for example, organic bases such as triethylamine, diisopropylethylamine, pyridine, 1,8-diazabicyclo[5.4.0]-7-undecene and the like; and inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, sodium amide and the like. The inert solvent includes, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as N,N-dimethylformamide, N-methylpyrrolidone and the like; acetonitrile; dimethyl sulfoxide; pyridine; and mixtures of solvents selected from these inert solvents.

Step 23:

Compound (32) of the present invention can be obtained by the same procedure as in Step 18.

Compounds (33), (34) and (35) of the present invention can be synthesized according also to the following reaction scheme 7.

Reaction Scheme 7



Step 24:

Compounds (33) and (34) of the present invention can be converted to each other by conventional protection and deprotection of the ester portion and the carboxylic acid portion (see Theodora W. Greene and Peter G. W. Wuts "Protective Groups in Organic Synthesis").

Step 25:

Compound (34) of the present invention can be converted to Compound (35) of the present invention by conventional amidation in the same manner as in Step 9. Compound (35) can be converted to Compound (34) by converting the amide portion of Compound (35) to a carboxylic acid by conventional hydrolysis (see Theodora W. Greene and Peter G. W. Wuts "Protective

Groups in Organic Synthesis").

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved. For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, disintegrators, pH-adjusting agents, solvents, etc.

The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or parenterally. The dose can be properly increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is concretely explained with reference to the following examples and test example, but is not limited thereto.

Example 1

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-quinoline (compound 1-01)

After 60% sodium hydride (an oil dispersion)

(79 mg) was washed with hexane and then suspended in N,N-dimethylformamide (3 mL), the suspension was cooled with ice. To the cooled suspension was added 8-(2,4-dichlorophenyl)-2-methyl-4-hydroxyquinoline (500 mg) all at once, and the resulting mixture was stirred under ice-cooling for 10 minutes and then at room temperature for another 30 minutes. To the solution thus obtained was added N-phenylbis(trifluoromethanesulfonimide) (703 mg) all at once, and the resulting mixture was stirred at room temperature for 30 minutes.

To the resultant reaction mixture were added sodium hydrogencarbonate (413 mg) and 4-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (533 mg), and the resulting mixture was vigorously stirred at 120℃ for 1 hour.

The reaction mixture thus obtained was cooled to room temperature and then separated with chloroform and water. The aqueous layer was extracted with chloroform and the combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1), and the crystals thus obtained were washed with methanol and then tetrahydrofuran to obtain the title compound (156 mg).

m.p. 263.5 - 265.5℃.

Table 1, Table 2, Table 7, Table 17 and Table 18 list the compound obtained in Example 1 and compounds obtained by the same procedure as in Example 1.

Example 2

Synthesis of 8-(2,4-dichlorophenyl)-4-(5-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-15)

(1) In phosphorus oxychloride (5 mL), 8-(2,4-dichlorophenyl)-2-methyl-4-hydroxyquinoline (2.0 g) was heated under reflux for 1 hour. The reaction mixture was cooled to room temperature and carefully poured into ice water, and the resulting mixture was separated with a saturated aqueous sodium hydrogencarbonate solution and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure to obtain a solid (2.1 g).

(2) A mixture of the solid (200 mg) obtained in (1), 5-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (121 mg), diisopropylethylamine (240 mg) and ethanol (1 mL)-water (0.075 mL) was allowed to react in a sealed tube at 80℃ for 10 days. The reaction mixture was cooled to room temperature, poured into a saturated aqueous sodium hydrogencarbonate solution, and then extracted three times with chloroform. The combined

organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1) and then crystallized from ethyl acetate to obtain the title compound (159 mg).

m.p. 230.0 - 232.0℃.

Table 1, Table 2, Tables 3 to 11, Table 13, Table 16, Table 19 and Table 20 list the compound obtained in Example 2 and compounds obtained by the same procedure as in Example 2.

Example 3

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-01)

(1) In N,N-dimethylformamide (50 mL), 4-chloro-8-(2,4-dichlorophenyl)-2-methylquinoline (3.3 g) obtained by the same procedure as in Example 2, (1) and 4-piperidone ethylene ketal (7.5 g) were stirred at 120℃ for 2 hours and then at 150℃ for 2 hours, and the resulting mixture was heated under reflux for 3.5 hours. The solvent was distilled off under reduced pressure, after which water and a saturated aqueous sodium hydrogencarbonate solution were added to the residue and the solid precipitated was collected by

filtration. The obtained solid was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1) to obtain 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (3.2 g).

m.p. 179.5 - 181.5℃.

(2) In a mixture of 1 M hydrochloric acid (30 mL) and tetrahydrofuran (15 mL), 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (3.2 g) was stirred at room temperature for 2 hours and then at 70℃ for 5.5 hours. The tetrahydrofuran was distilled off under reduced pressure, and the residue was made basic with a 41% aqueous sodium hydroxide solution under ice-cooling and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in ethanol (12.5 mL)-chloroform (6 mL), and potassium cyanide (5.4 g) was added thereto. To the mixture thus obtained was added acetic acid (4.4 mL) under ice-cooling over a period of 10 minutes, and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution and the organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was

filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in pyridine (15 mL), and phosphorus oxychloride (7.5 mL) was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 24 hours and then carefully poured into ice water. The reaction mixture thus treated was extracted three times with a mixed solvent of chloroform and methanol, and the combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 5 : 1) and then crystallized from diisopropyl ether to obtain 8-(2,4-dichlorophenyl)-2-methyl-4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)quinoline (1.0 g).

m.p. 177.5 - 179.5℃.

(3) In 96% formic acid (5 mL) was dissolved 8-(2,4-dichlorophenyl)-2-methyl-4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)quinoline (1.0 g), and hydrogen chloride gas was bubbled into the solution under ice-cooling to saturate the solution therewith. The reaction mixture was stirred at room temperature for 4 hours and then distilled under reduced pressure to remove the solvent. The residue was separated with chloroform and a saturated aqueous sodium hydrogen-

carbonate solution, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 10 : 1) and then recrystallized from tetrahydrofuran to obtain the title compound (174 mg).

m.p. 263.5 - 265.5℃.

Table 1 and Table 14 list the compound obtained in Example 3 and a compound obtained by the same procedure as in Example 3.

Example 4

Synthesis of 4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (compound 12-01)

(1) After 60% sodium hydride (an oil dispersion) (0.97 g) was washed with hexane and then suspended in N,N-dimethylformamide (10 mL), a solution of 1-(2,4-dichlorophenyl)-4-hydroxy-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (6.50 g) in N,N-dimethyl-formamide (90 mL) was added dropwise thereto. The resulting mixture was stirred at 40℃ for 30 minutes, after which N-phenylbis(trifluoromethanesulfonimide) (8.65 g) was added thereto all at once, followed by stirring at room temperature for 30 minutes. To the solution thus obtained was added 4-piperidone ethylene

ketal (16.4 g), and the reaction was carried out at 90℃ for 2 hours, at 100℃ for 1.5 hours, and then at 120℃ for 2.5 hours. After the reaction mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution was poured thereinto, followed by extraction with ethyl acetate, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure, and the residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 3 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (5.23 g).

(2) After 1-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]-pyridine (5.21 g) was stirred in a mixture of 4 M hydrochloric acid (60 mL) and tetrahydrofuran (60 mL) at room temperature for 2.5 hours, 6 M hydrochloric acid (30 mL) was added thereto and the resulting mixture was stirred overnight. After completion of the reaction, the reaction mixture was poured into a saturated aqueous sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The crystals thus

obtained were washed with ethyl acetate to obtain 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (3.83 g).

(3) In ethanol (10 mL)-chloroform (4 mL) was dissolved 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.55 g), and potassium cyanide (0.91 g) was added thereto. To the resulting mixture was added acetic acid (0.75 mL) under ice-cooling over a period of 15 minutes, followed by stirring at room temperature for 2 hours. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution and the organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in pyridine (6.4 mL), and phosphorus oxychloride (1.3 mL) was added thereto under ice-cooling. The reaction mixture was stirred at room temperature for 1 hour and then at 60℃ for 1 hour. The reaction mixture was carefully poured into ice water and extracted three times with ethyl acetate, and the combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-

ethyl acetate = 4 : 1) to obtain 4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.33 g).

(4) In methylene chloride (2.0 mL) was dissolved 4-(4-cyano-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.19 g), followed by adding thereto concentrated sulfuric acid (0.5 mL) under ice-cooling, and the resulting mixture was slowly heated to room temperature and then stirred overnight. The reaction mixture was separated with ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and the desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 30 : 1) and the crystals precipitated were washed with ethyl acetate to obtain the title compound (0.10 g).

m.p. 265.0 - 267.0℃.

Table 11 and Table 12 list the compound obtained in Example 4 and compounds obtained by the same procedure as in Example 4.

Example 5

Synthesis of 4-(5-carbamoyl-1,2,3,6-

tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (compound 12-09)

(1) After 60% sodium hydride (an oil dispersion) (79 mg) and a small amount of 35% potassium hydride (an oil dispersion) were washed twice with hexane, tetrahydrofuran (2.0 mL) and diethyl carbonate (0.21 g) were added thereto and the resulting mixture was heated at 80°C. Then, a solution of 1-(2,4-dichlorophenyl)-4-(4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.29 g) synthesized by the same procedure as in Example 4 in tetrahydrofuran (2.0 mL) was added dropwise thereto over a period of 10 minutes, and the resultant mixture was heated under reflux for 1.5 hours. After the reaction mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 4 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.14 g).

(2) In ethanol (3.0 mL) was dissolved 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-

oxopiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (0.13 g), and the solution was cooled to -15℃. Then, sodium boro hydride (26 mg) was added thereto and the resulting mixture was stirred overnight while being slowly heated to 0℃. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 50 : 1) to obtain 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-hydroxy-piperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (35 mg).

(3) In methylene chloride (1.5 mL) were dissolved 1-(2,4-dichlorophenyl)-4-(3-ethoxycarbonyl-4-hydroxypiperidin-1-yl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (53 mg), triethylamine (34 mg) and a small amount of 4-dimethylaminopyridine. Methanesulfonyl chloride (25 mg) was added thereto and the resulting mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium hydrogencarbonate solution was poured into the reaction mixture, which was then extracted three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate

was concentrated under reduced pressure. The residue was dissolved in benzene (1.0 mL), followed by adding thereto 1,8-diazabicyclo[5.4.0]-7-undecene (17 mg), and the resulting mixture was heated under reflux for 1 hour. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 5 : 1) to obtain 4-(5-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (27 mg).

(4) In ethanol (1.0 mL) was dissolved 4-(5-ethoxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-1-(2,4-dichlorophenyl)-2,3,6-trimethyl-1H-pyrrolo[2,3-b]pyridine (27 mg), followed by adding thereto a 1 M aqueous sodium hydroxide solution (1.0 mL), and the resulting mixture was stirred at room temperature for 8.5 hours. A saturated aqueous ammonium chloride solution was poured into the reaction mixture, which was then extracted three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was suspended in a mixed solvent of N,N-dimethylformamide (0.8 mL) and chloroform (0.2 ml), and 1-hydroxybenzotriazole monohydrate (18 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (23 mg) were added thereto. After the resulting mixture was stirred at room temperature for 40 minutes, a few drops of 28% aqueous ammonia solution was added thereto, and the mixture thus obtained was stirred at room temperature for 1.5 hours. A saturated aqueous sodium hydrogencarbonate solution was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 1 : 2) and crystallized from a mixed solvent of diisopropyl ether and ethyl acetate to obtain the title compound (6.0 mg).

Table 12 lists the compound obtained in Example 5.

Example 6

Synthesis of 5-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole (compound 15-01)

(1) After 2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole hydrochloride (6.0 g) and calcium carbonate (4.6 g) were suspended in a mixed solvent of chloroform (90 mL) and methanol (36 mL), benzyltrimethylammonium tribromide (7.2 g) was added thereto in small portions. The solids in the reaction mixture were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 9 : 1) to obtain 5-bromo-2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole (4.5 g).

(2) A mixture of 5-bromo-2-(N-ethyl-2,4-dichloroanilino)-4-methylthiazole (0.20 g), 5-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (178 mg), sodium hydrogencarbonate (94 mg) and ethanol (1.5 mL) was allowed to react in a sealed tube at 120℃ for 3 days. The reaction mixture was separated with water and chloroform and the aqueous layer was extracted with chloroform, after which the combined organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 20 : 1) and then crystallized from diisopropyl ether to obtain the title compound (34 mg).

m.p. 148.0 - 150.0℃.

Table 15 lists the compound obtained in Example 6.

Example 7

Synthesis of 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}-acetamide (compound 1-22) and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}-acetamide (compound 1-05)

(1) In a mixture of 1 M hydrochloric acid (26 mL) and tetrahydrofuran (13 mL), 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (2.6 g) obtained by the same procedure as in Example 3, (1) was stirred at room temperature for 2 hours and then at 70℃ for 5.5 hours. The tetrahydrofuran was distilled off under reduced pressure, and the residue was made basic with a 41% aqueous sodium hydroxide solution under ice-cooling and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure.

The resultant residue was dissolved in tetrahydrofuran (10 mL) and the resulting solution was added dropwise to a solution of Horner-Emmons reagent that had previously been prepared from ethyl diethylphosphonoacetate (2.05 g) and 60% sodium hydride (an oil dispersion) (293 mg) in tetrahydrofuran (10 mL),

under ice-cooling over a period of 20 minutes. The ice bath was removed, and the reaction mixture was stirred at room temperature for 30 minutes, quenched with a saturated aqueous ammonium chloride solution, and then extracted twice with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, after which the desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The resultant residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 9 : 1) and then crystallized from diisopropyl ether to obtain 8-(2,4-dichlorophenyl)-2-methyl-4-(4-ethoxycarbonyl-methylidenepiperidin-1-yl)quinoline (2.4 g).

(2) In a mixed solvent of 85% potassium hydroxide (1.3 g) and water (1.4 mL)-ethanol (8 mL), 8-(2,4-dichlorophenyl)-2-methyl-4-(4-ethoxycarbonyl-methylidenepiperidin-1-yl)quinoline (2.3 g) was stirred at 80℃ for 1 hour. The reaction mixture was neutralized with 3 M hydrochloric acid under ice-cooling and stirred under ice-cooling for 2 hours and then at room temperature for 30 minutes. The solid precipitated was collected by filtration to obtain a mixture (1.5 g) of 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}acetic acid and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}acetic acid.

(3) A mixture (400 mg) of 2-{1-[8-(2,4-

dichlorophenyl)-2-methylquinolin-4-yl]-piperidin-4-ylidene}acetic acid and 2-{1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridin-4-yl}acetic acid, 1-hydroxybenzotriazole monohydrate (215 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215 mg) were stirred in N,N-dimethylformamide (2 mL) at room temperature for 20 minutes. Then, a 28% aqueous ammonia solution (0.075 mL) was added thereto and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was separated with chloroform and water, and the organic layer was dried over anhydrous sodium sulfate. The desiccating agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was separated and purified twice by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-ethanol = 50 : 1), after which the purified products were crystallized from diethyl ether and diisopropyl ether, respectively, to obtain the title compound 1-22 (109 mg) and the title compound 1-05 (43 mg), respectively.

Compound 1-22: m.p. 225.0 - 227.0℃.

Compound 1-05: m.p. 160.0 - 162.0℃.

Table 1 and Table 16 list the compounds obtained in Example 7 and compounds obtained by the same procedure as in Example 7.

Example 8

Synthesis of 8-(2,4-dichlorophenyl)-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline

(1) After having been washed with hexane, 60% sodium hydride (an oil dispersion) (1.68 g) was suspended in N,N-dimethylformamide (20 mL). To the resulting suspension was added a suspension of 8-bromo-4-hydroxy-2-methylquinoline (10.0 g) in N,N-dimethylformamide (35 mL) at room temperature over a period of 10 minutes, followed by stirring at room temperature for 30 minutes. To the resultant solution was added N-phenylbis(trifluoromethanesulfonimide) (15.0 g) all at once, followed by stirring at room temperature for 1 hour.

To the resultant reaction mixture was added 4-piperidone ethylene ketal (11.0 g), and the resulting mixture was stirred at room temperature for 24 hours and heated under reflux at 60℃ for 4 hours and then for 2.5 hours. After 4-piperidone ethylene ketal (5.5 g) was added thereto, the mixture thus obtained was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature, poured into water (200 ml) and then stirred for 24 hours. The solid precipitated was collected by filtration and purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 5 : 1 to 3 : 1) to obtain 8-bromo-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (10.3 g), m.p. 156.0 - 158.0℃.

(2) Under a nitrogen atmosphere, 8-bromo-4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-methylquinoline (10.2 g), 2,4-dichlorophenylboric acid (6.0 g) and sodium carbonate (8.93 g) were suspended in a mixed solvent of deaerated water (24 mL), toluene (12 mL) and ethanol (12 mL), followed by adding thereto tetrakis-(triphenylphosphine)palladium (1.6 g), and the resulting mixture was heated under reflux for 16 hours. The reaction mixture was cooled to room temperature and separated with ethyl acetate and a saturated aqueous ammonium chloride solution. After the aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure and the resultant residue was crystallized from diisopropyl ether. The crystals were collected by filtration and washed with a small amount of diisopropyl ether to obtain the title compound (10.5 g).

m.p. 179.5 - 181.5℃.

Example 9

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-01)

(1) After having been washed with hexane, 60% sodium hydride (an oil dispersion) (1.0 g) was suspended in N-methylpyrrolidone (40 mL). To the

suspension was added 8-bromo-4-hydroxy-2-methyl-quinoline (5.0 g) all at once at room temperature, followed by stirring at room temperature for 1 hour. To the resulting solution was added N-phenylbis-(trifluoromethanesulfonimide) (15.0 g) all at once, followed by stirring at room temperature for 1 hour.

To the resultant reaction mixture were added sodium hydrogencarbonate (5.3 g) and 4-carbamoyl-1,2,3,6-tetrahydropyridine hydrochloride (6.8 g), and the resulting mixture was stirred at 130℃ for 30 minutes. After this reaction mixture was cooled to room temperature, water (100 mL) was added thereto, followed by stirring at room temperature for 2 hours. The solid precipitated was collected by filtration and then washed with water to obtain 8-bromo-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methyl-quinoline (4.8 g).

m.p. 225.0 - 227.0℃.

(2) Under a nitrogen atmosphere, 8-bromo-2-methyl-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)quinoline (4.7 g), 2,4-dichlorophenylboric acid (2.9 g) and sodium carbonate (4.5 g) were suspended in a mixed solvent of deaerated water (14 mL), toluene (7 mL) and ethanol (7 mL), followed by adding thereto tetrakis(triphenylphosphine)palladium (0.81 g), and the resulting mixture was heated under reflux for 5 hours. The reaction mixture was cooled to room temperature and stirred at room temperature for 3 hours. The solid

precipitated was collected by filtration and washed with a water-ethanol (2 : 1) mixed solvent (30 mL) and then ethanol (30 mL) to obtain the title compound (4.7 g).

Table 1 lists the compound obtained in Example 9.

Example 10

Synthesis of 8-(2,4-dichlorophenyl)-4-(4-isopropyloxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-14)

(1) After having been washed with hexane, 60% sodium hydride (an oil dispersion) (1.0 g) was suspended in N-methylpyrrolidone (30 mL). To the suspension was added 8-bromo-4-hydroxy-2-methylquinoline (5.0 g) all at once at room temperature, followed by stirring at room temperature for 1 hour. To the resulting solution was added N-phenylbis(trifluoromethanesulfonimide) (9.0 g) all at once, followed by stirring at room temperature for 1 hour.

To the resultant reaction mixture was added 4-isopropyloxycarbonyl-1,2,3,6-tetrahydropyridine (8.5 g), and the resulting mixture was stirred overnight at room temperature. This reaction mixture was poured into a mixture of water and ethyl acetate to be separated. After the aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent

was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane-ethyl acetate = 9 : 1), and the solid thus obtained was washed with a mixture of diisopropyl ether and hexane to obtain 8-bromo-4-(4-isopropyloxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (6.0 g).

m.p. 130.0 - 131.0℃.

(2) Under a nitrogen atmosphere, 8-bromo-4-(4-isopropyloxycarbonyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (5.9 g), 2,4-dichlorophenylboric acid (3.2 g) and sodium carbonate (4.8 g) were suspended in a mixed solvent of deaerated water (15 mL), toluene (7.5 mL) and ethanol (7.5 mL), followed by adding thereto tetrakis(triphenylphosphine)palladium (0.88 g), and the resulting mixture was heated under reflux for 5 hours. The reaction mixture was cooled to room temperature to be separated. After the aqueous phase was extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate. The desiccating agent was filtered off, after which the filtrate was concentrated under reduced pressure and the resultant residue was crystallized from diisopropyl ether. The crystals were collected by filtration and washed with a small amount of diisopropyl ether to obtain the title compound (5.3 g).

m.p. 131.0 - 133.0℃.

Table 1 lists the compound obtained in Example 10.

Example 11

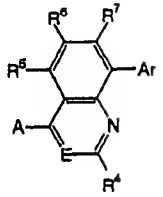
Synthesis of 8-(2,4-dichlorophenyl)-4-(4-carboxy-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (compound 1-11)

In concentrated hydrochloric acid (10 mL) was suspended 8-(2,4-dichlorophenyl)-4-(4-carbamoyl-1,2,3,6-tetrahydropyridin-1-yl)-2-methylquinoline (0.10 g), and the suspension was heated under reflux for 1 hour. After the reaction mixture was concentrated under reduced pressure, 28% aqueous ammonia (2 mL) was added thereto, followed by concentration under reduced pressure. The residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform-methanol = 20 : 1 to 10 : 1), and the solid precipitated was washed with ethyl acetate to obtain the title compound (74 mg).

m.p. 218.0 - 220.0℃.

Table 1 lists the compound obtained in Example 11.

Table 1[*1]



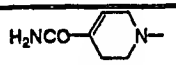
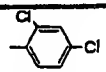
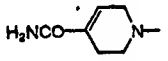
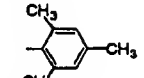
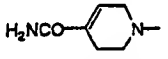
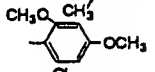
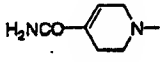
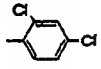
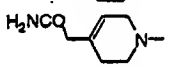
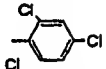
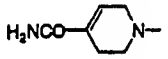
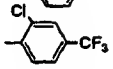
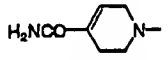
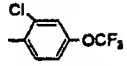
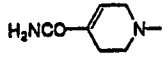
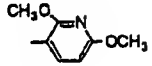
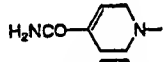
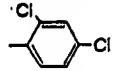
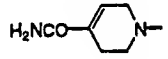
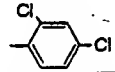
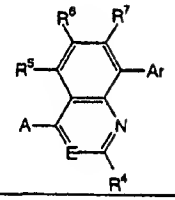
Com.No.	Ex.No.	A	E	R^4	R^5	R^6	R^7	Ar	Melting point (℃) (solvent for crystallization)
1-01	1,3,9		CH	CH_3	H	H	H		263.5-265.5(MeOH)
1-02	2		CH	CH_3	H	H	H		220.5-222.5(AcOEt)
1-03	2		CH	CH_3	H	H	H		242.0-244.0(MeOH)
1-04	2		N	CH_3	H	H	H		220.0-222.0(Et_2O)
1-05	7		CH	CH_3	H	H	H		160.0-162.0(IPE)
1-06	1		CH	CH_3	H	H	H		235.0-236.0(MeOH)
1-07	1		CH	CH_3	H	H	H		215.0-216.0(MeOH)
1-08	1		CH	CH_3	H	H	H		228.0-230.0(MeOH)
1-09	1		CH	CH_3	H	Cl	H		256.0-258.0(MeOH)
1-10	1		CH	CH_3	H	CH_3	H		252.0-254.0(MeOH)

Table 1[*1] (Cont'd)



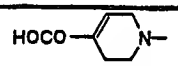
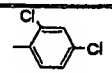
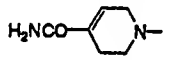
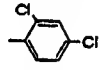
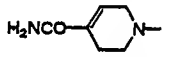
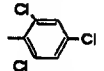
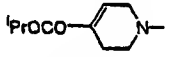
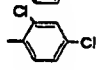
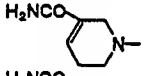
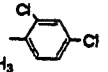
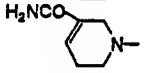
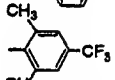
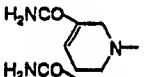
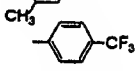
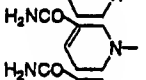
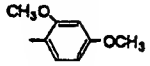
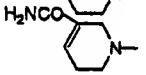
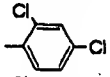
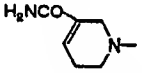
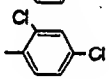
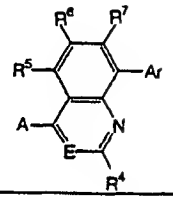
Com.No.	Ex.No.	A	E	R^4	R^5	R^6	R^7	Ar	Melting point (℃) (solvent for crystallization)
1-11	11		CH	CH_3	H	H	H		218.0-220.0(AcOEt)
1-12	1		CH	CH_3	H	F	H		273.0-275.0(MeOH)
1-13	1		CH	CH_3	H	OCF_3	H		235.0-236.0(MeOH)
1-14	10		CH	CH_3	H	H	H		131.0-133.0(IPE/hexane)
1-15	2		CH	CH_3	H	H	H		230.0-232.0(AcOEt)
1-16	2		CH	CH_3	H	H	H		144.5-146.5(AcOEt)
1-17	2		CH	CH_3	H	H	H		140.5-142.5(Et_2O)
1-18	2		CH	CH_3	H	H	H		185.0-187.0(EtOH)
1-19	2		N	CH_3	H	H	H		Amorphous[*2]
1-20	1		CH	CH_3	H	F	H		237.0-238.0(MeOH)

Table 1[*1] (Cont'd)



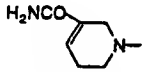
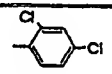
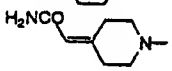
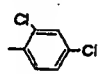
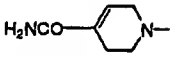
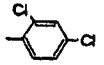
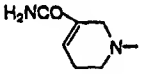
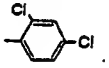
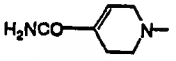
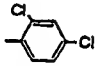
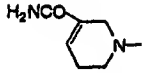
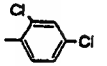
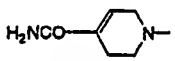
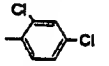
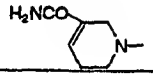
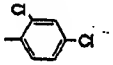
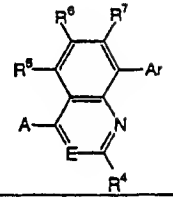
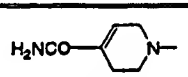
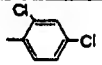
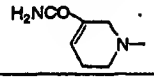
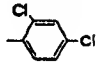
Com.No.	Ex.No.	A	E	R^4	R^5	R^6	R^7	Ar	Melting point (°C) (solvent for crystallization)
1-21	1		CH	CH_3	H	OCF_3	H		170.0-173.0(EtOH)[*3]
1-22	7		CH	CH_3	H	H	H		225.0-227.0(Et_2O)
1-23	1		CH	CH_3	H	$N(CH_3)_2$	H		202.0-204.0(EtOH)
1-24	1		CH	CH_3	H	$N(CH_3)_2$	H		187.0-189.0(IPA/AcOEt)[*3]
1-25	1		CH	CH_3	F	H	H		244.0-246.0(EtOH)
1-26	1		CH	CH_3	F	H	H		214.0-216.0(EtOH)
1-27	1		CH	H	H	H	H		>235(decomposed)(EtOH)
1-28	1		CH	H	H	H	H		220.5-222.5(EtOH)

Table 1*1 (Cont'd)



Com.No.	Ex.No.	A	E	R^4	R^5	R^6	R^7	Ar	Melting point (°C) (solvent for crystallization)
1-29	1		CH	NH_2	H	H	H		>230(decomposed)(MeOH)
1-30	1		CH	NH_2	H	H	H		155.0-158.5(IPA/Et_2O)

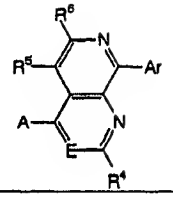
*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; MeOH = methanol, EtOH = ethanol, AcOEt = ethyl acetate, Et_2O = diethyl ether

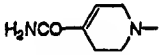
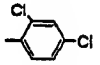
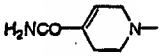
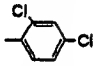
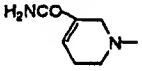
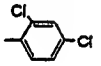
*2: ^1H NMR (200MHz, $CDCl_3$); δ 2.41(3H, s), 2.48-2.66(2H, m), 3.72-3.95(2H, m), 4.34-4.46(2H, m), 6.76-6.87(1H, m), 7.05(1H, br, s), 7.42(1H, d, J=8.4Hz), 7.47-7.63(3H, m), 7.68(1H, dd, J=1.3, 7.3Hz), 7.72(1H, d, J=1.8Hz), 8.04(1H, dd, J=1.3, 8.4Hz).

MS(ES, Pos); 435$(M+Na)^+$, 437$(M+Na+2)^+$, 439$(M+Na+4)^+$

*3: HCl salt

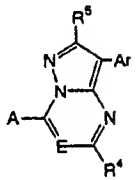
Table 2*1

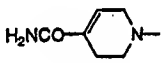
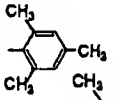
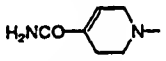
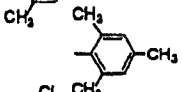
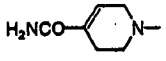
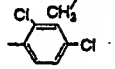
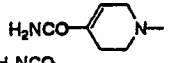
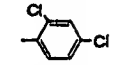
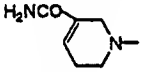
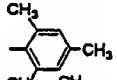
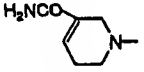
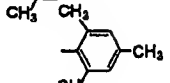
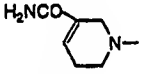
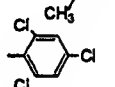
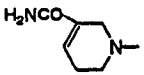
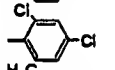
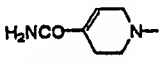
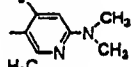
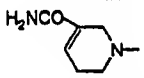
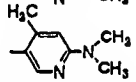


Com.No.	Ex.No.	A	E	R^4	R^5	R^6	Ar	Melting point (°C) (solvent for crystallization)
2-01	2		N	CH_3	H	H		221.0-223.0(AcOEt)
2-02	1		CH	CH_3	H	H		277.0-279.0(AcOEt)
2-03	2		N	CH_3	H	H		100.0-102.0(IPE)

*1: Com.No. = compound number, Ex.No. = example number,
solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

Table 3*1

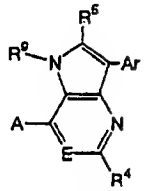


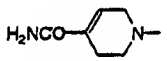
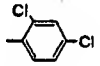
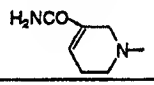
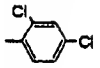
Com.No.	Ex.No.	A	E	R^4	R^5	Ar	Melting point (°C) (solvent for crystallization)
3-01	2		CH	CH_3	CH_3		245.0-247.0(AcOEt/IPE)
3-02	2		N	CH_3	CH_3		245.0-247.0(AcOEt/IPE)
3-03	2		CH	CH_3	CH_3		252.0-254.0(AcOEt)
3-04	2		N	CH_3	CH_3		255.0-257.0(AcOEt)
3-05	2		CH	CH_3	CH_3		187.0-189.0(AcOEt/IPE)
3-06	2		N	CH_3	CH_3		145.0-147.0(EtOH/AcOEt)*2
3-07	2		CH	CH_3	CH_3		150.0-152.0(AcOEt)
3-08	2		N	CH_3	CH_3		209.0-211.0(AcOEt)
3-09	2		CH	CH_3	CH_3		245.0-247.0(AcOEt/IPE)
3-10	2		CH	CH_3	CH_3		253.0-255.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; EtOH = ethanol, AcOEt = ethyl acetate, IPE = diisopropyl ether

*2: HCl salt

Table 4*1



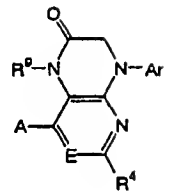
Com.No.	Ex.No.	A	E	R^4	R^5	R^9	Ar	Melting point (℃) (solvent for crystallization)
4-01	2		N	CH_3	H	CH_3		Amorphous*2
4-02	2		N	CH_3	H	CH_3		169.0-171.0(AcOEt/Et_2O)

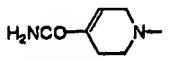
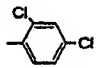
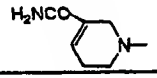
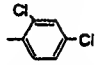
*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, Et_2O = diethyl ether

*2: ^1H NMR (200MHz, $CDCl_3$); δ 2.57-2.75(2H, m), 2.67(3H, s), 3.55(2H, t, J=5.7Hz), 4.01(3H, s), 4.08-4.18(2H, m), 6.70-6.82(1H, m), 7.35(1H, dd, J=2.1, 8.6Hz), 7.49(1H, d, J=2.1Hz), 7.70(1H, s), 8.09(1H, d, J=8.6Hz).

MS(ES, Pos.); 416$(M+1)^+$, 418$(M+3)^+$

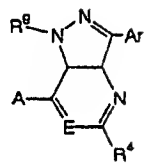
Table 5*1

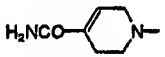
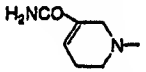


Com.No.	Ex.No.	A	E	R^4	R^9	Ar	Melting point (℃) (solvent for crystallization)
5-01	2		N	CH_3	CH_3		267.0-269.0(AcOEt)
5-02	2		N	CH_3	CH_3		165.0-167.0(AcOEt)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate

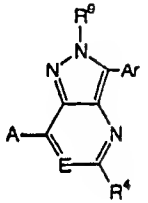
Table 6*1

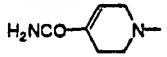
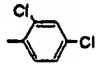
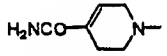
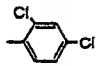
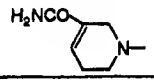
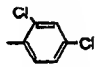


Com.No.	Ex.No.	A	E	R^4	R^9	Ar	Melting point (°C) (solvent for crystallization)
6-01	2		N	CH_3	CH_3		221.0-223.0(Et_2O)
6-02	2		N	CH_3	CH_3		209.0-211.0(Et_2O)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; Et_2O = diethyl ether

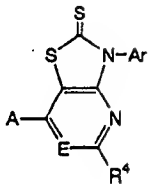
Table 7*1

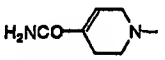
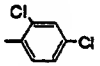
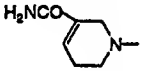
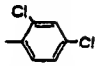


Com.No.	Ex.No.	A	E	R^4	R^9	Ar	Melting point (°C) (solvent for crystallization)
7-01	2		N	CH_3	CH_3		266.0-268.0(AcOEt)
7-02	1		CH	CH_3	CH_3		231.0-233.0(AcOEt)
7-03	2		N	CH_3	CH_3		211.0-213.0(AcOEt)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, Et_2O = diethyl ether

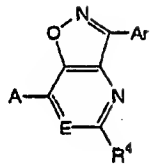
Table 8*1

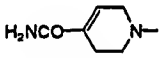
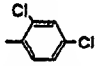
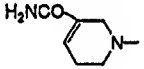
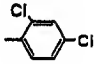


Com.No.	Ex.No.	A	E	R^4	Ar	Melting point (°C) (solvent for crystallization)
8-01	2		N	CH_3		283.0-285.0(AcOEt)
8-02	2		N	CH_3		186.0-188.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

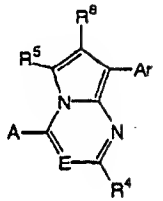
Table 9*1

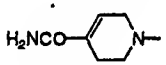
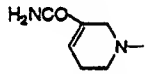


Com.No.	Ex.No.	A	E	R^4	Ar	Melting point (℃) (solvent for crystallization)
9-01	2		N	CH_3		191.0-193.0(AcOEt/IPE)
9-02	2		N	CH_3		217.0-219.0(AcOEt)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

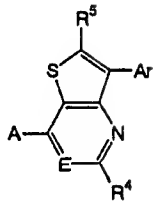
Table 10*1

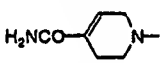
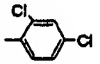
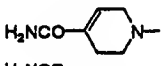
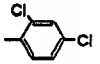
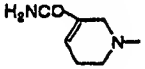
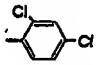


Com.No.	Ex.No.	A	E	R^4	R^5	R^6	Ar	Melting point (°C) (solvent for crystallization)
10-01	2		CH	CH_3	H	H		242.0-244.0(Et_2O)
10-02	2		CH	CH_3	H	H		208.0-210.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, Et_2O = diethyl ether, IPE = diisopropyl ether

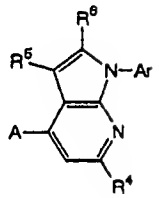
Table 11*1



Com.No.	Ex.No.	A	E	R^4	R^5	Ar	Melting point (°C) (solvent for crystallization)
11-01	2		N	CH_3	H		220.0-222.0(THF/hexane)
11-02	4		CH	CH_3	H		238.0-240.0($CHCl_3$/MeOH)
11-03	2		N	CH_3	H		216.0-218.0(THF/hexane)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; MeOH = methanol, THF = tetrahydrofuran

Table 12[*1]



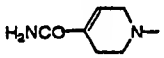
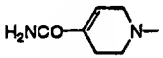
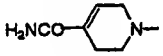
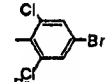
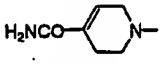
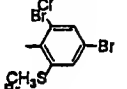
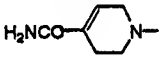
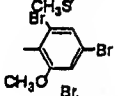
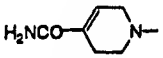
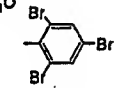
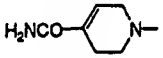
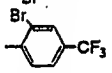
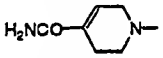
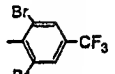
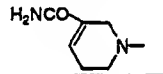
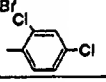
Com.No.	Ex.No.	A	R^4	R^5	R^6	Ar	Melting point (°C) (solvent for crystallization)
12-01	4		CH_3	CH_3	CH_3		265.0-267.0(AcOEt)
12-02	4		CH_3	CH_3	CH_3		273.0-275.0(AcOEt)
12-03	4		CH_3	CH_3	CH_3		267.0-269.0(AcOEt)
12-04	4		CH_3	CH_3	CH_3		208.0-210.0(AcOEt)
12-05	4		CH_3	CH_3	CH_3		170.0-172.0(AcOEt/IPE)
12-06	4		CH_3	CH_3	CH_3		162.0-164.0(AcOEt)
12-07	4		CH_3	CH_3	CH_3		249.0-251.0(AcOEt)
12-08	4		CH_3	CH_3	CH_3		203.0-205.0($CHCl_3$/IPE)
12-09	5		CH_3	CH_3	CH_3		Amorphous[*2]

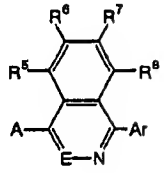
Table 12 (Cont'd)

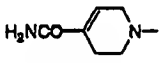
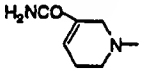
*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

*2: 1H NMR (200MHz, CDCl3); δ 2.06(3H, s), 2.40(3H, s), 2.45(3H, br. s), 2.48-2.60(2H, m), 3.21-3.43(2H, m), 3.86-3.96(2H, m), 6.54(1H, s), 6.70-6.77(1H, m), 7.29(1H, d, J=8.5Hz), 7.39(1H, dd, J=2.3, 8.5Hz), 7.57(1H, d, J=2.3Hz).

MS(ES, Pos); $429(M+1)^+$, $431(M+3)^+$

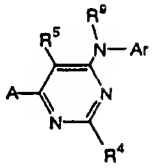
Table 13*1

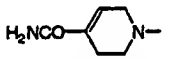
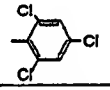


Com.No.	Ex.No.	A	E	R^5	R^6	R^7	R^8	Ar	Melting point (°C) (solvent for crystallization)
13-01	2		N	H	H	H	H		294.0-296.0(THF/$CHCl_3$)
13-02	2		N	H	H	H	H		133.0-135.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether, THF = tetrahydrofuran

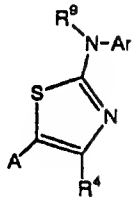
Table 14*1

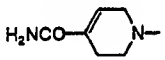


Com.No.	Ex.No.	A	R^4	R^5	R^9	Ar	Melting point (°C) (solvent for crystallization)
14-01	3		CH_3	CH_3	H		241.0-243.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

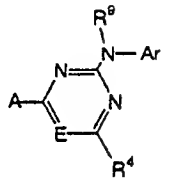
Table 15*1

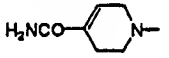
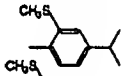
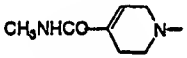
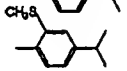
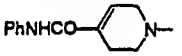
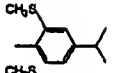
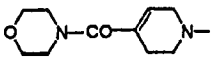
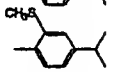
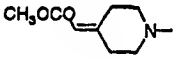
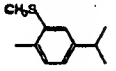
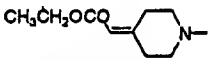
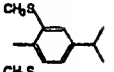
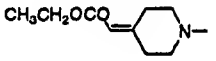
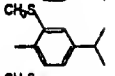
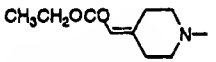
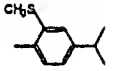
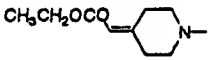
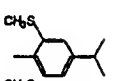
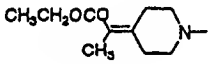
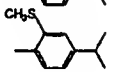


Com.No.	Ex.No.	A	R^4	R^9	Ar	Melting point (°C) (solvent for crystallization)
15-01	6		CH_3	CH_2CH_3		148.0-150.0(IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; IPE = diisopropyl ether

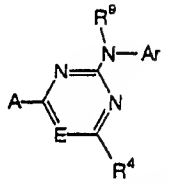
Table 16*1

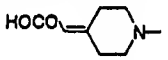
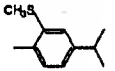
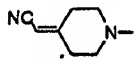
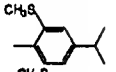
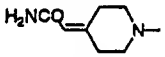
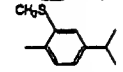
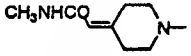
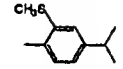
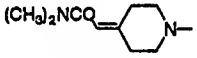
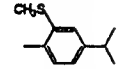
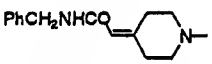
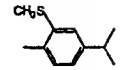
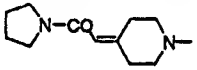
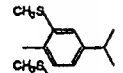
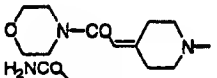
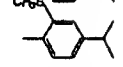
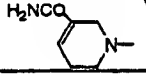
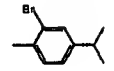


Com.No.	Ex.No.	A	E	R^4	R^9	Ar	Melting point (°C) (solvent for crystallization)
16-01	2		CH	CH_3	CH_2CH_3		100.0-102.0(Et_2O/hexane)
16-02	2		CH	CH_3	CH_2CH_3		211.0-213.0(Et2O)
16-03	2		CH	CH_3	CH_2CH_3		140.0-142.0(AcOEt)
16-04	2		CH	CH_3	CH_2CH_3		138.0-140.0(Et_2O/hexane)
16-05	7		CH	CH_3	CH_2CH_3		oil*2
16-06	7		CH	CH_3	CH_2CH_3		oil*3
16-07	7		CH	CH_3			oil*4
16-08	7		CH	CH_3			oil*5
16-09	7		CH	CH_3			oil*6
16-10	7		CH	CH_3	CH_2CH_3		oil*7

- Cont'd -

Table 16*1



Com.No.	Ex.No.	A	E	R^4	R^9	Ar	Melting point (°C) (solvent for crystallization)
16-11	7		CH	CH_3	CH_2CH_3		oil*8
16-12	7		CH	CH_3	CH_2CH_3		oil*9
16-13	7		CH	CH_3	CH_2CH_3		oil*10
16-14	7		CH	CH_3	CH_2CH_3		oil*11
16-15	7		CH	CH_3	CH_2CH_3		oil*12
16-16	7		CH	CH_3	CH_2CH_3		oil*13
16-17	7		CH	CH_3	CH_2CH_3		oil*14
16-18	7		CH	CH_3	CH_2CH_3		oil*15
16-19	2		N	CH_3	CH_2CH_3		117.0-119.0(IPE)

- Cont'd -

Table 16 (Cont'd)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, Et2O = diethyl ether, IPE = diisopropyl ether

*2: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.29(6H, d, J=6.8Hz), 2.12-2.34(2H, m), 2.20(3H, s), 2.36(3H, s), 2.80-3.04(3H, m), 3.30-4.39(6H, m), 3.69(3H, s), 5.70(1H, s), 5.81(1H, s), 6.95-7.18(3H, m).

MS(ES, Pos); $455(M+1)^+$

*3: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.02-1.38(12H, m), 2.03-2.43(2H, m), 2.21(3H, s), 2.37(3H, s), 2.72-3.08(3H, m), 3.17-4.35(6H, m), 4.15(2H, q, J=7.0Hz), 5.69(1H, s), 5.81(1H, s), 6.94-7.17(3H, m).

MS(ES, Pos); $469(M+1)^+$

*4: ^{1}H NMR (200MHz, $CDCl_3$); δ 0.03-0.48(4H, m), 1.04-1.39(10H, m), 2.08-2.34(2H, m), 2.19(3H, s), 2.33(3H, s), 2.80-3.07(3H, m), 3.15-3.74(5H, m), 4.02-4.33(1H, m), 4.15(2H, q, J=7.0Hz), 5.69(1H, s), 5.80(1H, s), 6.96-7.22(3H, m).

MS(SIMS, Pos); $495(M+1)^+$

*5: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20-1.35(9H, m), 2.10-2.33(2H, m), 2.19(3H, s), 2.36(3H, s), 2.78-3.06(3H, m), 3.30-3.74(4H, m), 3.90-4.30(1H, m), 4.15(2H, q, J=7.0Hz), 4.65-5.20(3H, m), 5.70(1H, s), 5.82(1H, s), 5.92-6.20(1H, m), 6.94-7.17(3H, m).

MS(SIMS, Pos); $481(M+1)^+$

*6: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.19-1.36(9H, m), 2.08-2.38(3H, m), 2.22(3H, s), 2.38(3H, s), 2.80-3.05(3H, m), 3.35-3.77(4H, m), 4.00-4.30(1H, m), 4.16(2H, q, J=7.0Hz), 5.00-5.37(1H, m), 5.71(1H, s), 5.87(1H, s), 6.98-7.33(3H, m).

MS(SIMS, Pos); $479(M+1)^+$

*7: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.13-1.38(12H, m), 1.87(3H, s), 2.18(3H, s), 2.26-2.77(4H, m), 2.36(3H, s), 2.95(1H, sept, J=7.0Hz), 3.33-4.32(6H, m), 4.19(2H, q, J=7.0Hz), 5.74(1H, s), 6.96-7.17(3H, m).

MS(ES, Pos); 483$(M+1)^+$

*8: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.21(3H, t, J=7.0Hz), 1.28(6H, d, J=7.0Hz), 2.04-2.41(2H, m), 2.21(3H, s), 2.36(3H, s), 2.80-3.06(3H, m), 3.23-4.39(6H, m), 5.60(1H, s), 5.81(1H, s), 6.01(1H br. s), 6.93-7.15(3H, m).

MS(FAB, Pos); 441$(M+1)^+$

*9: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.21(3H, t, J=7.0Hz), 1.29(6H, d, J=7.0Hz), 2.10-2.35(2H, m), 2.23(3H, s), 2.37(3H, s), 2.41-2.59(2H, m), 2.94(1H, sept, J=7.0Hz), 3.31-4.38(6H, m), 5.14(1H, s), 5.83(1H, s), 6.98-7.18(3H, m).

MS(ES, Pos); 422$(M+1)^+$

*10: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.27(6H, d, J=7.0Hz), 2.00-2.32(2H, m), 2.19(3H, s), 2.35(3H, s), 2.80-3.05(3H, m), 3.36-4.38(6H, m), 5.36-5.71(3H, m), 5.73(1H, s), 6.96-7.18(3H, m).

MS(FAB, Pos); 440$(M+1)^+$

*11: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.27(6H, d, J=7.0Hz), 2.06-2.32(2H, m), 2.19(3H, s), 2.35(3H, s), 2.72-3.06(3H, m), 2.81(3H, d, J=5.0Hz), 3.23-4.35(6H, m), 5.35-5.60(1H, m), 5.55(1H, s), 5.80(1H, s), 6.92-7.16(3H, m).

MS(FAB, Pos); 454$(M+1)^+$

*12: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.26(6H, d, J=7.0Hz), 2.06-2.30(2H, m), 2.20(3H, s), 2.36(3H, s), 2.46-2.61(2H, m), 2.80-3.10(1H, m), 2.97(3H, s), 3.01(3H, s), 3.31-4.39(6H, m), 5.80(1H, s), 6.94-7.17(3H, m).

MS(FAB, Pos); 468(M+1)$^+$

*13: HCl salt, ^{1}H NMR (200MHz, $CDCl_3$); δ 1.03-1.53(9H, m), 1.60-4.88(14H, m), 2.41(3H, s), 4.45(2H, d, J=5.0Hz), 5.56-6.62(3H, m), 6.84-7.59(8H, m), 13.37(1H, br s).

MS(FAB, Pos); 530(M+1)$^+$

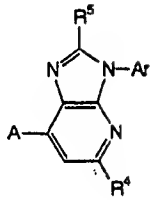
*14: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.28(6H, d, J=7.0Hz), 1.75-2.03(4H, m), 2.09-2.32(2H, s), 2.20(3H, s), 2.35(3H, s), 2.70-2.90(2H, m), 2.95(1H, sept, J=7.0Hz), 3.33-4.33(10H, m), 5.81(1H, s), 5.83(1H, s), 6.96-7.15(3H, m).

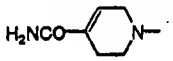
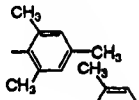
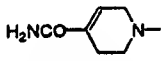
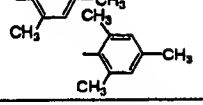
MS(FAB, Pos); 494(M+1)$^+$

*15: ^{1}H NMR (200MHz, $CDCl_3$); δ 1.20(3H, t, J=7.0Hz), 1.27(6H, d, J=7.0Hz), 2.10-2.30(2H, m), 2.20(3H, s), 2.36(3H, s), 2.41-2.60(2H, m), 2.96(1H, sept, J=7.0Hz), 3.27-4.40(14H, m), 5.81(1H, s), 6.95-7.16(3H, m).

MS(FAB, Pos); 510(M+1)$^+$

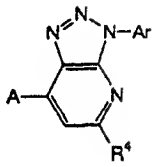
Table 17*1

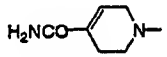
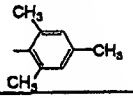


Com.No.	Ex.No.	A	R^4	R^5	Ar	Melting point (°C) (solvent for crystallization)
17-01	1		CH_3	H		209.0-211.0(AcOEt/IPE)
17-02	1		CH_3	CH_2CH_3		202.0-204.0(AcOEt/IPE)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate, IPE = diisopropyl ether

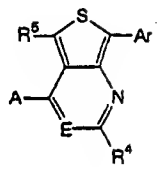
Table 18*1

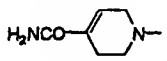
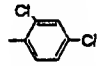


Com.No.	Ex.No.	A	R^4	Ar	Melting point (°C) (solvent for crystallization)
18-01	1		CH_3		230.0-231.0(EtOH)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; EtOH = ethanol

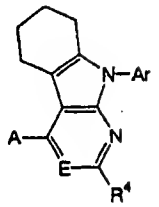
Table 19*1

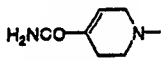
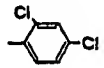
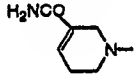
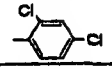


Com.No.	Ex.No.	A	E	R^4	R^5	Ar	Melting point (°C) (solvent for crystallization)
19-01	2		N	CH_3	H		213.0-215.0(EtOH)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; EtOH = ethanol

Table 20*1



Com.No.	Ex.No.	A	E	R^4	Ar	Melting point (℃) (solvent for crystallization)
20-01	2		N	CH_3		247.0-249.0(AcOEt)
20-02	2		N	CH_3		181.0-183.0(AcOEt)

*1: Com.No. = compound number, Ex.No. = example number, solvent for crystallization; AcOEt = ethyl acetate

Test Example [CRF receptor bonding test]

Rat frontal cortex membranes or monkey amygdaloid body membranes were used as a receptor preparation.

^{125}I-CRF was used as ^{125}I-labeled ligand.

Bonding reaction using the ^{125}I-labeled ligand was carried out by the following method described in The Journal of Neuroscience, 7, 88 (1987).

Preparation of a receptor membranes:

Rat frontal cortex or monkey amygdaloid body was homogenized in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$ and 2 mM EDTA and centrifuged at 48,000 x g, and the precipitate was washed once with Tris-HCl buffer. The washed precipitate was suspended in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml aprotinin, to obtain a membrane preparation.

CRF receptor bonding test:

The membrane preparation (0.3 mg protein/ml), ^{125}I-CRF (0.2 nM) and a test drug were reacted at 25℃ for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) treated with 0.3% polyethylene-imine, and the glass filter was washed three times with phosphate-buffered saline containing 0.01% Triton X-100. After the washing, the radioactivity of the filter paper was measured in a gamma counter.

The amount of ^{125}I-CRF bonded when the reaction was carried out in the presence of 1 μM CRF was taken as the degree of nonspecific binding of ^{125}I-CRF, and the difference between the total degree of ^{125}I-CRF binding and the degree of nonspecific ^{125}I-CRF binding was taken as the degree of specific ^{125}I-CRF binding. An inhibition curve was obtained by reacting a definite concentration (0.2 nM) of ^{125}I-CRF with various concentrations of each test drug under the conditions described above. A concentration of the test drug at which binding of ^{125}I-CRF is inhibited by 50% (IC_{50}) was determined from the inhibition curve.

As a result, it was found that compounds 1-01, 1-02, 1-05, 1-06, 1-07, 1-09, 1-10, 1-12, 1-15, 1-16, 12-01 to 12-09, 16-05, 16-06 and 16-12 can be exemplified as typical compounds having an IC_{50} value of 500 nM or less.

INDUSTRIAL APPLICABILITY

According to the present invention, compounds having a high affinity for CRF receptors have been provided. These compounds are effective against diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral

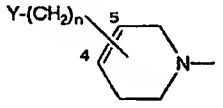
ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, etc.

CLAIMS

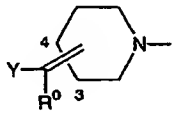
1. A tetrahydropyridino or piperidino heterocyclic derivative represented by the formula [I]:

A-Het [I]

wherein A is a group represented by the following formula [II] or [III]:



[II]



[III]

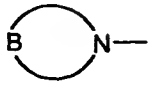
wherein the position of substitution by the $Y-(CH_2)_n-$ group of the group represented by the formula [II] is 4-position or 5-position, the position of substitution by the $Y-C(R^0)=$ group of the group represented by the formula [III] is 3-position or 4-position,

R^0 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group,

n is an integer of 0 to 5, and

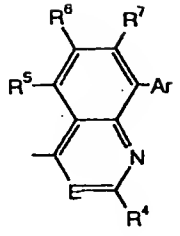
Y is a cyano group, a group represented by the formula $-CONR^1(R^2)$ (wherein each of R^1 and R^2, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{3-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group, or R^1 and R^2, when taken together with the adjacent nitrogen atom, represent a 5- to 8-membered saturated heterocyclic

group represented by the formula:

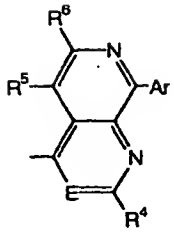


(wherein B is CH_2, NH, N-C_{1-5}alkyl, N-C_{3-8}cycloalkyl, N-C_{1-5}alkyl-C_{3-8}cycloalkyl, O or S)) or a group represented by the formula $-CO_2R^3$ (wherein R^3 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{1-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group), and

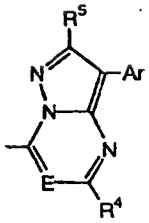
Het is any of heterocyclic groups represented by the following formulas form(01) to form(20):



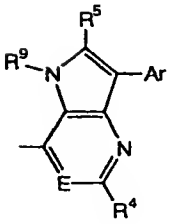
form(01)



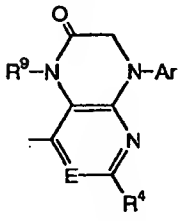
form(02)



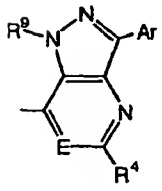
form(03)



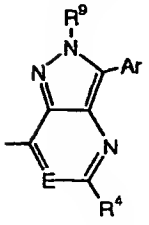
form(04)



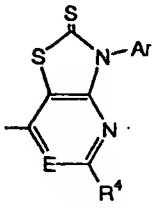
form(05)



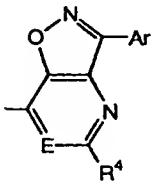
form(06)



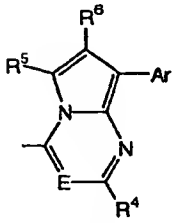
form(07)



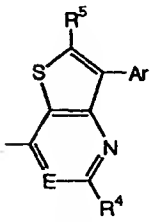
form(08)



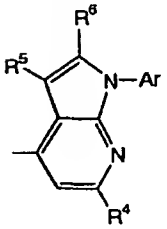
form(09)



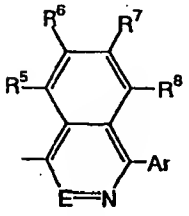
form(10)



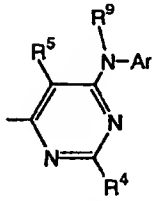
form(11)



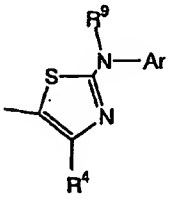
form(12)



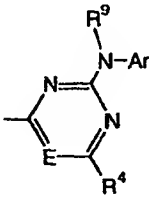
form(13)



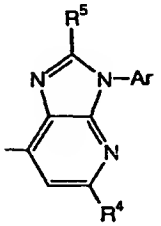
form(14)



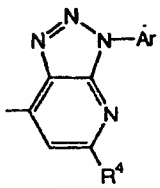
form(15)



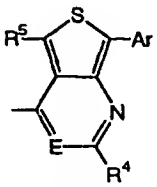
form(16)



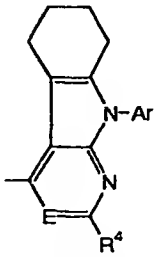
form(17)



form(18)



form(19)



form(20)

wherein E is CH or N,

R^4 is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a hydroxyl group, a C_{1-5}alkoxy group, a C_{3-8}cycloalkyloxy group, or a group represented by the formula $-N(R^{10})R^{11}$ (wherein each of R^{10} and R^{11}, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group),

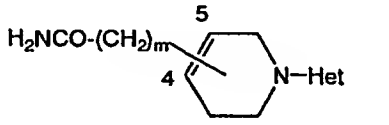
each of R^5, R^6, R^7 and R^8, which may be the same or different, is a hydrogen atom, a halogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a hydroxyl group, a C_{1-5}alkoxy group, a C_{3-8}cycloalkyloxy group, a group represented by the formula $-N(R^{12})R^{13}$ (wherein each of R^{12} and R^{13}, which may be the same or different, is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group), a group represented by the formula $-CO_2R^{14}$ (wherein R^{14} is a hydrogen atom, a C_{1-5}alkyl group, a C_{3-8}cycloalkyl group, a C_{3-8}cycloalkyl-C_{1-5}alkyl group, a C_{1-5}alkoxy-C_{1-5}alkyl group, a C_{3-8}cycloalkyloxy-C_{1-5}alkyl group or a phenyl group), a cyano group, a nitro group, a C_{1-5}alkylthio group, a trifluoromethyl group or a trifluoromethoxy group,

R^9 is a hydrogen atom, a C_{1-5}alkyl group, a C_{2-5}alkenyl group, a C_{2-5}alkynyl group, a C_{3-8}cycloalkyl group or a C_{3-8}cycloalkyl-C_{1-5}alkyl group, and

Ar is an aryl or heteroaryl group unsubstituted or substituted with 1 to 3 substituents which may

be the same or different and are selected from halogen atoms, C_{1-5}alkyl groups, C_{1-5}alkoxy groups, C_{1-5}alkylthio groups, trifluoromethyl group, trifluoromethoxy group and groups represented by the formula $-N(R^{15})R^{16}$ (wherein each of R^{15} and R^{16}, which may be the same or different, is a hydrogen atom or a C_{1-5}alkyl group); or a pharmaceutically acceptable salt thereof or its hydrate.

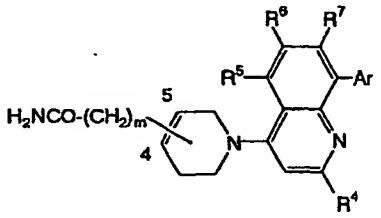
2. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 1, which is a compound represented by the formula [IV]:



[IV]

wherein Het is as defined above, and m is 0 or 1.

3. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 2, which is a compound represented by the formula [V]:



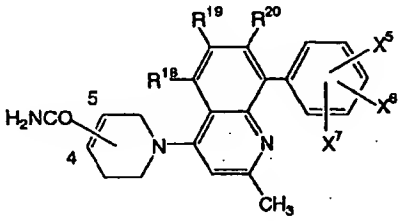
[V]

wherein R^4, R^5, R^6, R^7, Ar and m are as defined above.

4. The tetrahydropyridino heterocyclic derivative or a pharmaceutically acceptable salt thereof or its hydrate according to Claim 3, wherein m in the

formula [V] is 0.

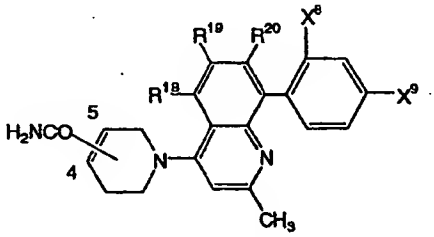
5. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 4, which is a compound represented by the formula [VI]:



[VI]

wherein each of R^{18}, R^{19} and R^{20}, which may be the same or different, is a hydrogen atom, a methyl group, a fluorine atom or a chlorine atom, and each of X^5, X^6 and X^7, which may be the same or different, is a hydrogen atom, a methyl group, a chlorine atom, a trifluoromethyl group or a trifluoromethoxy group.

6. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 5, which is a compound represented by the formula [VII]:

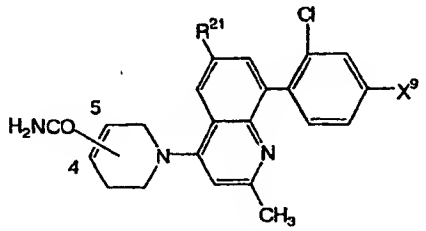


[VII]

wherein R^{18}, R^{19} and R^{20} are as defined above, and each of X^8 and X^9, which may be the same or different, is a chlorine atom, a trifluoromethyl group or a trifluoro-

methoxy group.

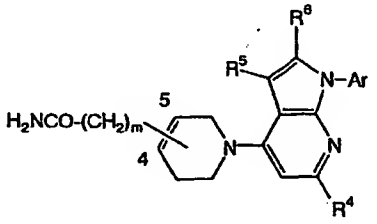
7. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 6, which is a compound represented by the formula [VIII]:



[VIII]

wherein X^9 is as defined above, and R^{21} is a hydrogen atom, a chlorine atom or a methyl group.

8. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 2, which is a compound represented by the formula [IX]:



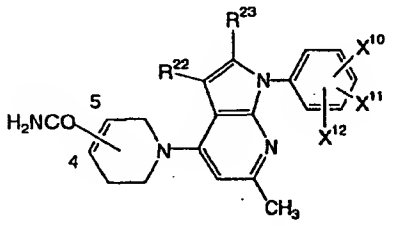
[IX]

wherein R^4, R^5, R^6, Ar and m are as defined above.

9. The tetrahydropyridino heterocyclic derivative or a pharmaceutically acceptable salt thereof or its hydrate according to Claim 8, wherein m in the formula [IX] is 0.

10. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof

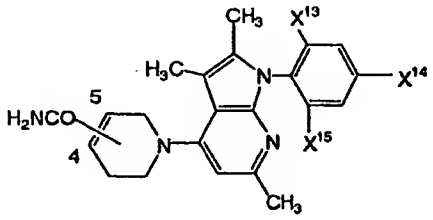
or its hydrate according to Claim 9, which is a compound represented by the formula [X]:



[X]

wherein each of R^{22} and R^{23}, which may be the same or different, is a hydrogen atom or a methyl group, and each of X^{10}, X^{11} and X^{12}, which may be the same or different, is a hydrogen atom, a chlorine atom, a bromine atom, a methoxy group, a methylthio group or a trifluoromethyl group.

11. The tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to Claim 9, which is a compound represented by the formula [XI]:



[XI]

wherein X^{13} is a chlorine atom or a bromine atom, X^{14} is a chlorine atom, a bromine atom or a trifluoromethyl group, and X^{15} is a hydrogen atom, a chlorine atom, a bromine atom, a methoxy group, a methylthio group or a trifluoromethyl group.

12. An antagonist against CRF receptors,

comprising a tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to any one of Claims 1 to 11, as an active ingredient.

13. Use of a tetrahydropyridino heterocyclic derivative, a pharmaceutically acceptable salt thereof or its hydrate according to any one of Claims 1 to 11, as an antagonist against CRF receptors.